

Chapter #1 – Anatomy of Retroperitoneum, Adrenals, Kidneys, and Ureters

THE RETROPERITONEUM

Posterior Abdominal Wall

Describe the lumbodorsal fascia

- surrounds **sacrospinalis & quadratus lumborum** muscles, making posterior abdominal wall
- originates from spinous processes of lumbar vertebrae & extends anteriorly and cranially
- **separates into 3 layers:**
 - 1) posterior → posterior covering of sacrospinalis & origin of latissimus dorsi
 - 2) middle → b/w sacrospinalis posteriorly & quadratus lumborum anteriorly
 - 3) anterior → anterior covering of quadratus lumborum and forms posterior margin of retroperitoneum
- 3 layers connect laterally with **transversus abdominis muscle**

What is the significance of the dorsal lumbotomy incision?

- vertical incision lateral to border of sacrospinalis & quadratus lumborum } Petit's triangle
→ sacrospinalis is middle layer
- allows entrance to retroperitoneum without violation of musculature } **no muscles are cut**

What are the muscles of the lateral flank?

- External oblique → from lower ribs, moving lateral to medial going caudally
→ attaches to iliac crest caudally and rectus sheath anteriorly
- Internal oblique → from lower ribs, moving medial to lateral going caudally
→ attaches to iliac crest caudally and lumbodorsal fascia posteriorly
- Transversus abdominis → from lumbodorsal fascia, running directly transversely
→ attaches anteriorly and medially to rectus sheath
- transversalis fascia lies directly beneath transversus abdominis m. and above retroperitoneum

Describe the Psoas and Iliacus muscles

- Psoas → originates from T12 to L5 and is covered by the psoas fascia
→ 50% have psoas minor, which sits medial to psoas major
- Iliacus → attaches to the inner aspect of the iliac wing (lateral to psoas)
- psoas & iliacus join caudally to form iliopsoas muscle, which inserts into lesser trochanter

What are the limits of the pleura?

- anteriorly → 8th rib
- midaxillary line → 10th rib
- posteriorly → 12th rib

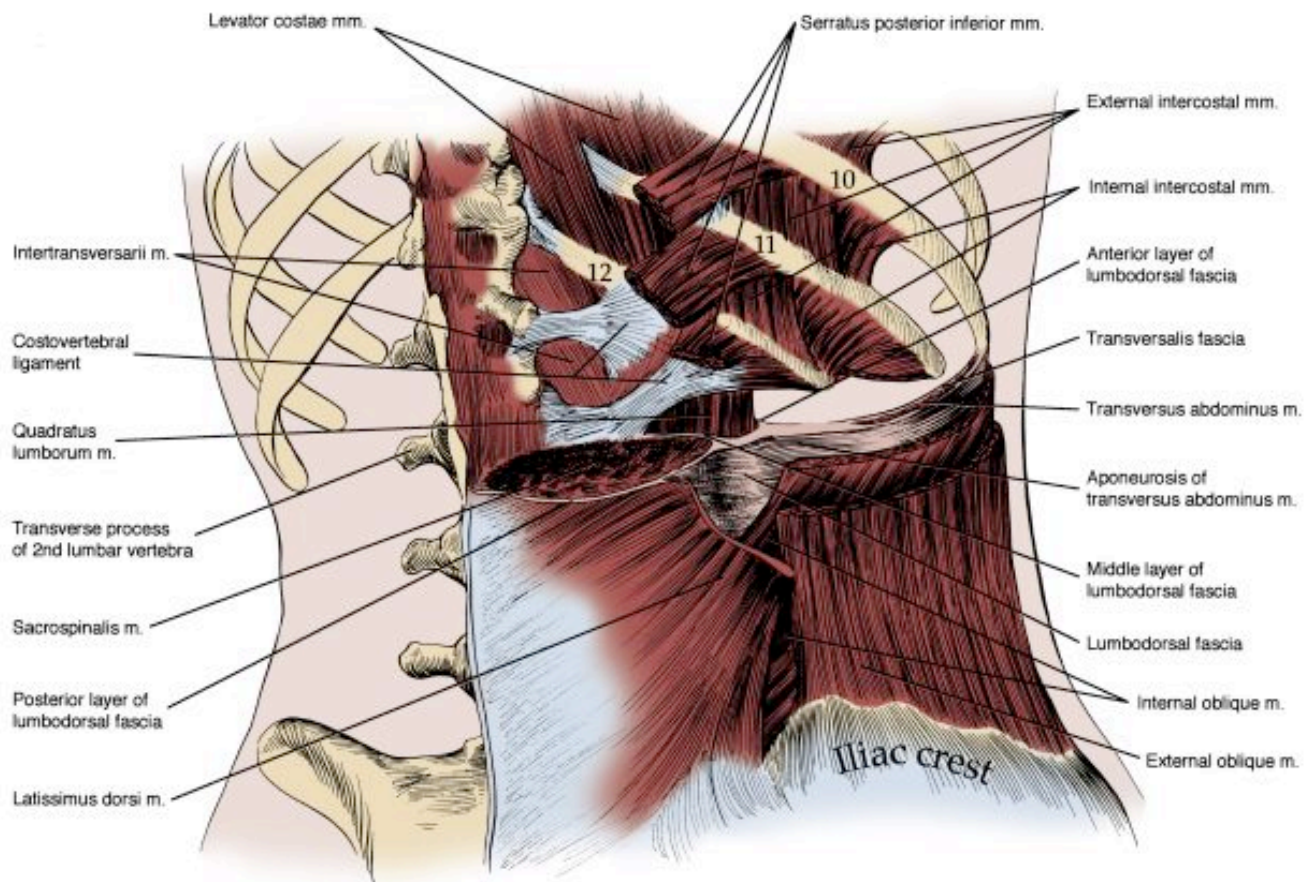
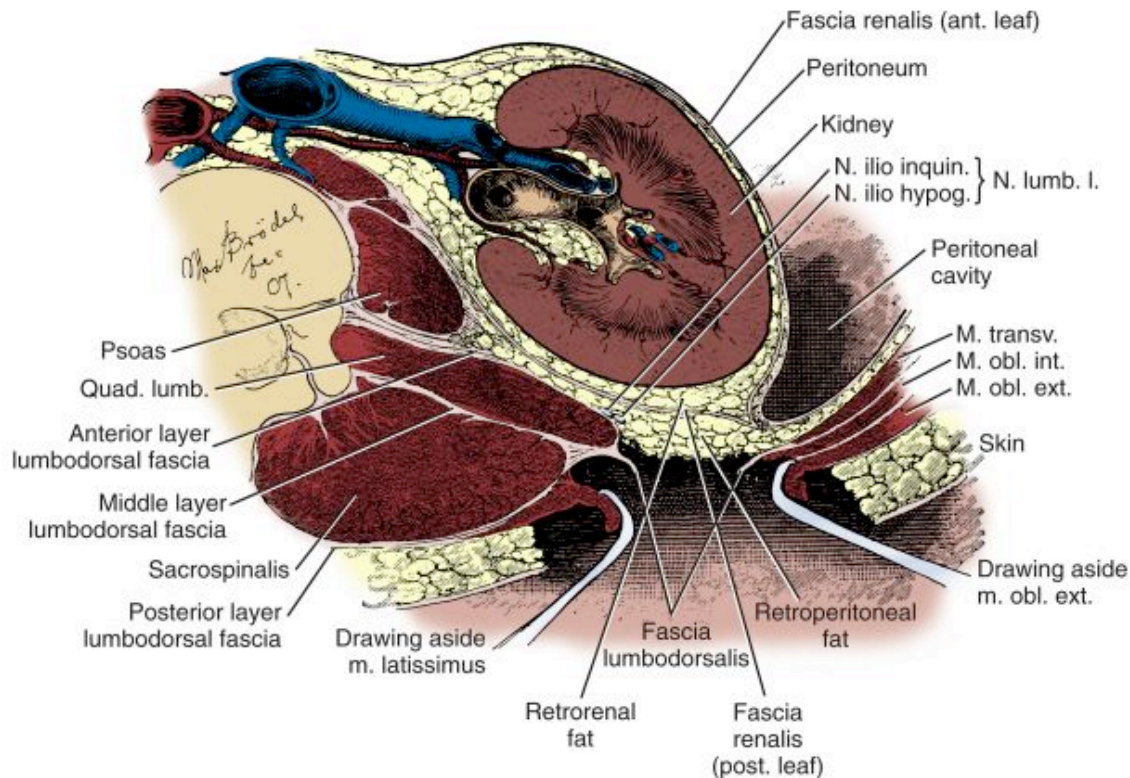


Table 1-1 -- Musculature of the Posterior and Lateral Abdominal Wall

<i>Muscle</i>	<i>Origin</i>	<i>Insertion</i>	<i>Function</i>
Sacrospinalis	Sacrum and lumbar vertebrae	Lower ribs and thoracic vertebrae	Extension of the spine
Quadratus lumborum	5th lumbar vertebra	1st through 4th lumbar vertebrae, 12th rib	Depress and stabilize 12th rib, lateral bending of the trunk
External oblique	Lower eight ribs	Lateral lip of iliac crest, aponeurosis ending in midline raphe	Compress abdominal contents, flexion of the trunk
Internal oblique	Lumbodorsal fascia, iliac crest	Lower four ribs, aponeurosis ending in linea alba	Compress abdominal contents, flexion of the trunk
Transversus abdominis	Lumbodorsal fascia, medial lip of iliac crest	Aponeurosis ending in linea alba	Compress abdominal contents
Psoas	12th thoracic through 5th lumbar vertebrae	Lesser trochanter of femur	Flexion of the hip
Iliacus	Inner aspect of iliac pelvic wing	Lesser trochanter of femur	Flexion of the hip



→ LUMBODORSAL INCISION } no muscles cut

Great Vessels

What are the branches of the aorta?

→ enters at T12 via aortic hiatus and bifurcates at level of L4

- 1) paired inferior phrenics → inferior diaphragm & superior portion of adrenal
- 2) celiac trunk → stomach, liver, spleen, GB, duodenum
 - common hepatic, L gastric, & splenic arteries
 - gastroduodenal a. comes off common hepatic, then gives off R gastroepiploic a.
 - L gastroepiploic a. comes off splenic artery
- 3) paired adrenals
- 4) SMA → entire small bowel & majority of colon
 - communicates with celiac trunk vasculature via pancreaticoduodenal artery
 - this can supply liver retrogradely if celiac trunk tied off (trauma)
- 5) paired renals → overlie L2
- 6) paired gonadals → can be ligated due to collaterals (deferential & cremasteric; uterine)
- 7) IMA → distal end of transverse colon, descending, sigmoid, & rectum
 - can be ligated due to collaterals (SMA, middle hemorrhoidal, inferior hemorrhoidal)
- 8) 4 paired lumbar → posterior body wall & spine
- 9) middle sacral → posterior branch just before bifurcation
 - supplies rectum & anterior sacrum

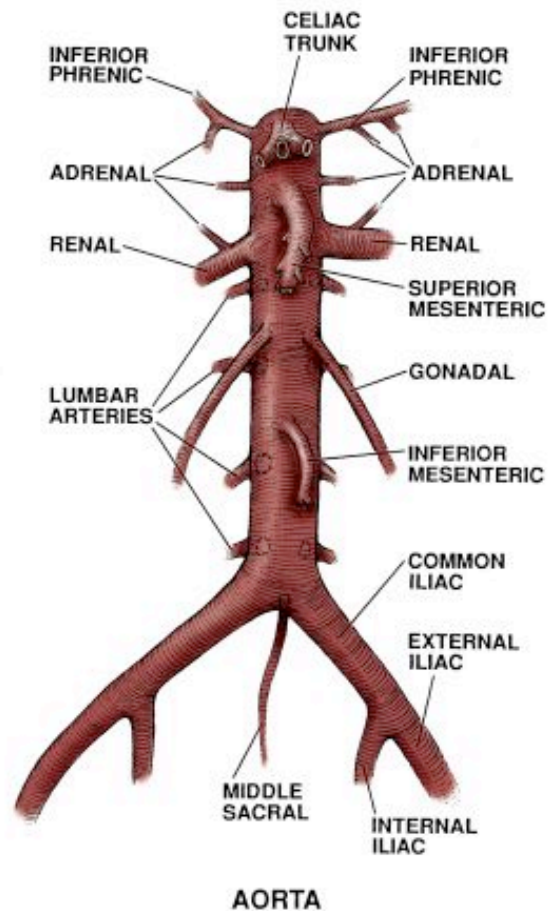
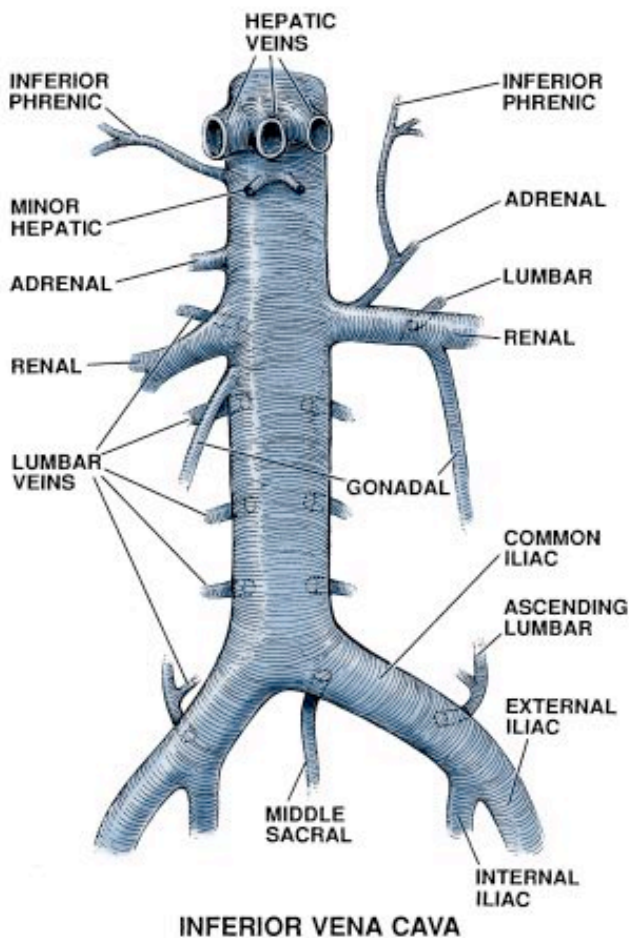
What is the course of the gonadal artery?

- male → crosses anterior to IVC on right
 - crosses over ureter and exits retroperitoneum at internal inguinal ring
- female → crosses anterior to IVC on right
 - crosses over ureter moving laterally then crosses back over external iliacs into pelvis, where it proceeds via suspensory ligament to ovary

What are the tributaries to the IVC?

→ **from the confluence of the common iliacs at L5, which lies posterior and to the right of the aortic bifurcation**

- 1) middle sacral → posterior tributary at jxn of common iliac veins
- 2) paired lumbar → generally parallel to lumbar arteries
→ also connects IVC to azygous on R and hemiazygous on L, providing alternate venous drainage of retroperitoneum
- 3) gonadal veins → course similar to gonadal arteries but different once close to IVC
→ drains into IVC on R, into left renal vein on L
→ **runs lateral to ureter**
- 4) paired renal veins → generally directly anterior to renal arteries
→ R is short (2-4cm), L is long (6-10cm)
→ small minority will have R gonadal or lumbar entering R renal vein posteriorly
→ L renal vein gets gonadal inferiorly, lumbar posteriorly, & adrenal superiorly before crossing anterior to the aorta, just under SMA
→ L renal vein can be retroaortic on occasion
- 5) adrenal → R adrenal goes directly into IVC but posteriorly, making dissection difficult
→ L adrenal drains into L renal vein
- 6) short hepatic
- 7) inferior phrenic → R drains into IVC on posterolateral aspect, L drains into L renal
- 8) hepatic veins → 3 large trunks from liver



Nervous System

What autonomic nerves lie within the retroperitoneum?

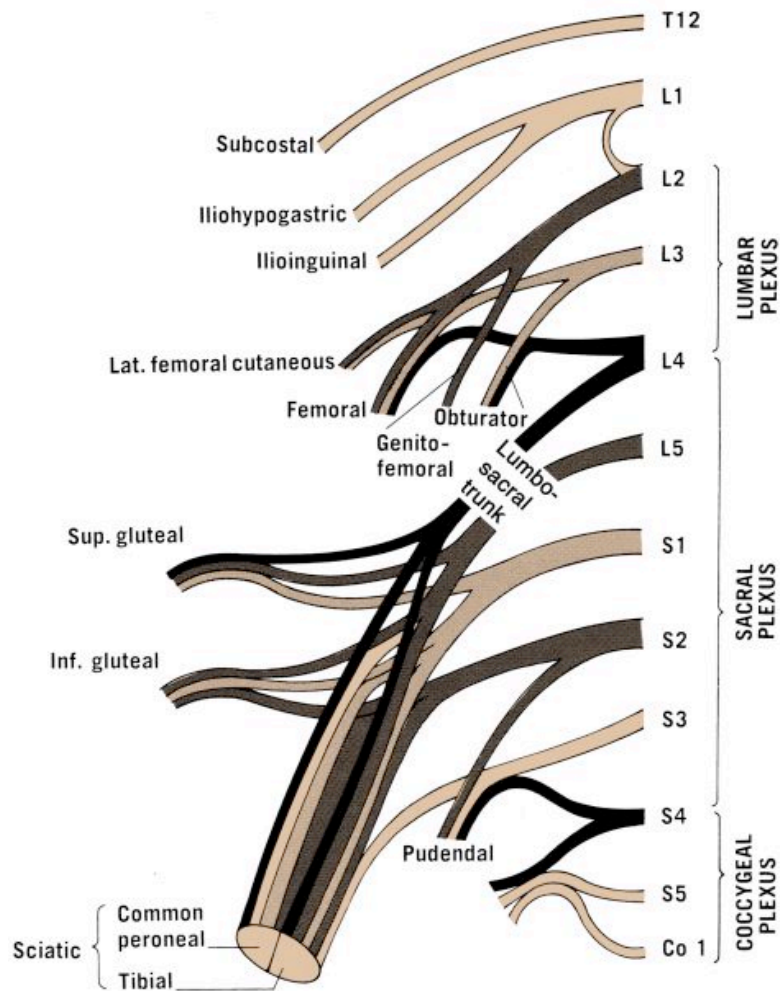
- **sympathetic**
 - preganglionic fibers **originate from T and L spine (T1-L3)**
 - enter retroperitoneum via paired sympathetic chains & lumbar spinal nerves
 - from sympathetic chain, preganglionic fibers have 3 different courses;
 - 1) travels into **autonomic plexuses (splanchnic nerves)** where they synapse with postganglionic fibers
 - these proceed to the abdo viscera
 - 2) synapses within **sympathetic chain**, where postganglionic fibers are sent to body wall & lower extremities
 - 3) travels directly to **adrenal medulla**, controlling release of catecholamines
- **parasympathetics**
 - preganglionic fibers **originate from C and S spine**
 - also get input from **vagus nerve**
 - travel into **aortic autonomic plexuses**, where they synapse with postganglionic fibers that are distributed to the viscera and organs

What are the major autonomic nerve plexuses?

- 1) celiac } largest plexus; innervates kidney, adrenal, renal pelvis, and ureter
- 2) superior hypogastric } innervates pelvic urinary and genital tract
 - } lies on aorta anterior to bifurcation, extending down on anterior surface of L5
- 3) inferior hypogastric } contiguous with superior hypogastric plexus and extends into pelvis

What somatic nerves lie within the retroperitoneum?

- **arises from the lumbosacral plexus (T12-L5)**
- superior branches form within and pierce the psoas inferior branches pass medial to the psoas
- Subcostal (T12) → extends laterally beneath 12th rib
- Iliohypogastric (L1) → *motor* to internal oblique & transversus
 - *sensory* to posterolateral gluteal skin
- **Ilioinguinal** (L1) → *motor* to internal oblique & transversus
 - *sensory* to upper medial thigh & base of penis/anterior scrotum/mons pubis
- Lateral Cutaneous nerve of thigh (L2-L3) → *sensory* to anterior and lateral thigh to knee
- **Genitofemoral** (L1-L2) → lies directly atop and parallels psoas
 - *motor* to cremaster & dartos muscles in scrotum (genital branch only)
 - *sensory* to scrotum/mons/labia majora & skin of upper thigh (genital & femoral branches)
- **Femoral** (L2-L4) → hidden by psoas until it exits abdomen just lateral to femoral artery
 - *motor* to psoas, iliacus, and large muscles of anterior thigh (quads)
 - *sensory* to anterior thigh & medial leg
 - can be injured by retractor placed on inguinal ligament (can't extend knee, numb on anterior thigh)
- **Obturator** (L2-L4) → *motor* to adductor muscles of thigh (longus, brevis, gracilis, pectineus)
 - *sensory* to medial thigh
 - can be injured during RP pelvic LN dissection (can't adduct leg)
- Sciatic (L4-S3) → **body's largest nerve**
 - *motor & sensory* to legs (common peroneal + tibial)
- Pudendal (S2-S4) → branches include inferior rectal, perineal, dorsal penile nerves

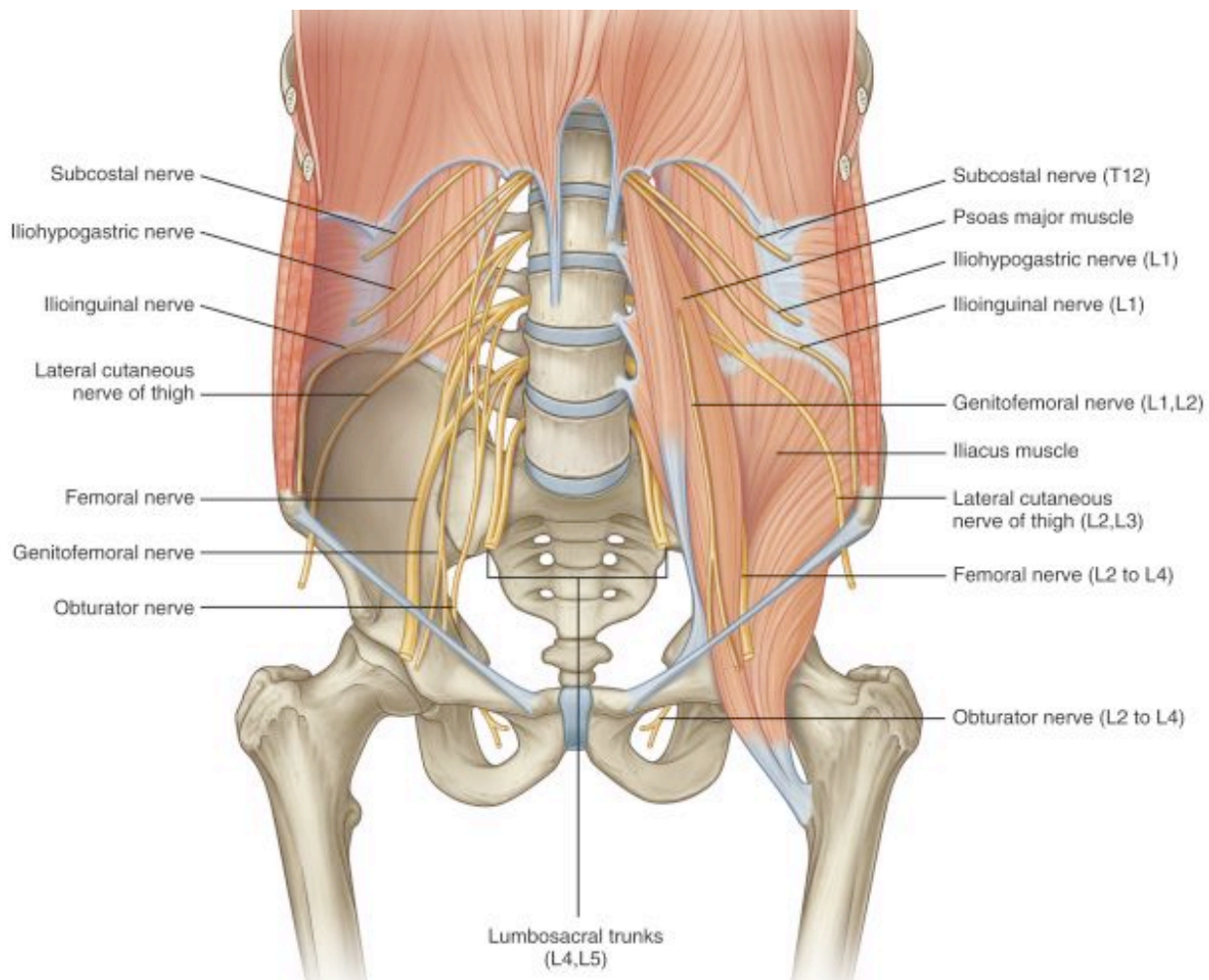


→ LUMBOSACRAL NERVOUS PLEXUS

Table 1-3 -- Branches of the Lumbosacral Plexus

Branch	Origin	Spinal Segments	Function: Motor	Function: Sensory
Iliohypogastric	Anterior ramus L1	L1	Internal oblique and transversus abdominis	Posterolateral gluteal skin and skin in pubic region
Ilioinguinal	Anterior ramus L1	L1	Internal oblique and transversus abdominis	Skin in the upper medial thigh, and either the skin over the root of the penis and anterior scrotum or the mons pubis and labium majus
Genitofemoral	Anterior rami L1 and L2	L1, L2	Genital branch—male cremasteric muscle	Genital branch—skin of anterior scrotum or skin of mons pubis and labium majus; femoral branch—skin of upper anterior thigh
Lateral cutaneous nerve of thigh	Anterior rami L2 and L3	L2, L3		Skin on anterior and lateral thigh to the knee
Obturator	Anterior rami L2 to L4	L2 to L4	Obturator externus, pectineus, and muscles in medial compartment of thigh	Skin on medial aspect of the thigh
Femoral	Anterior rami L2 to L4	L2 to L4	Iliacus, pectineus, and muscles in anterior compartment of thigh	Skin on anterior thigh and medial surface of leg

From Drake RL, Vogl W, Mitchell AWM: Gray's Anatomy for Students. Philadelphia, Elsevier, 2005, p 340.



→ LUMBAR PLEXUS IN POSTERIOR ABDOMINAL REGION

Lymphatics

What is the lymphatic drainage of the lower extremities, perineum and external genitalia?

- external iliac nodes → common iliac nodes → vertical lumbar lymphatic chains
- lumbar lymphatics are important as the primary drainage from the kidneys & testes
- flow is cranial and also R → L
- GI lymphatics follow the vasculature (IMA, SMA, celiac)
- eventually these lymphatics join posterior to aorta, between aorta and IVC, at level of L1 or L2 to form **cisterna chyli (R side of aorta), which becomes the thoracic duct**
→ **cisternal chyli is a retrocrural structure**
- thoracic duct turns toward left thorax at level of T4 to join venous system at jxn of left jugular and subclavian veins

What is the lymphatic drainage of the testes?

- right → right **inter-aortocaval nodes** & paracaval
→ small amount of drainage to left para-aortic nodes
- left → left **para-aortic nodes**

Duodenum, Pancreas, Colon

What are the 4 sections of the duodenum?

- 1) ascending → 5cm and is closely related to GB
- 2) descending → lies immediately anterior to R renal hilum & pelvis and surrounds head of pancreas
(also receives common bile duct)
→ often Kocherized to access R kidney, R renal pelvis & upper abdo structures
- 3) horizontal → crosses anterior to the IVC
- 4) distal ascending → cross anterior to aorta to transition into jejunum

Where is the pancreas situated?

- head lies on medial aspect of 2nd portion of duodenum, close to R renal hilum/pelvis
- tail lies close to L adrenal gland and upper pole of L kidney
- splenic artery & vein travel laterally from the celiac along the posterior aspect of the pancreas

Which aspects of the colon are retroperitoneal?

- ascending & descending colon
- hepatic & splenic flexure overlie the ipsilateral kidney
- hepatocolic and splenocolic ligaments tether the liver and spleen to the colon

THE ADRENALS

Describe the gross anatomy of the adrenal glands

- 3-5cm in adults, weighing about 5g and yellow-gold in colour
- enclosed within Gerota's fascia and separated from the UP of the kidney by a layer of connective tissue
- R → more superior & pyramidal in shape; often has a retrocaval wing
- L → more inferior & crescentic; lies more medial to upper pole

What is the composition of the adrenal gland?

- embryologically distinct from kidney
- **adrenal cortex** makes up 90% of adrenal mass and is of **mesodermal origin**
 - zona glomerulosa → mineralocorticoids (eg aldosterone)
 - zona fasciculata → glucocorticoids (eg cortisol) & sex steroids
 - zona reticularis → sex steroids (eg androgens)
- **adrenal medulla** is made up of chromaffin cells derived from **neural crest origin**
 - innervated directly by preganglionic sympathetic fibers
 - catecholamine release is controlled by sympathetics

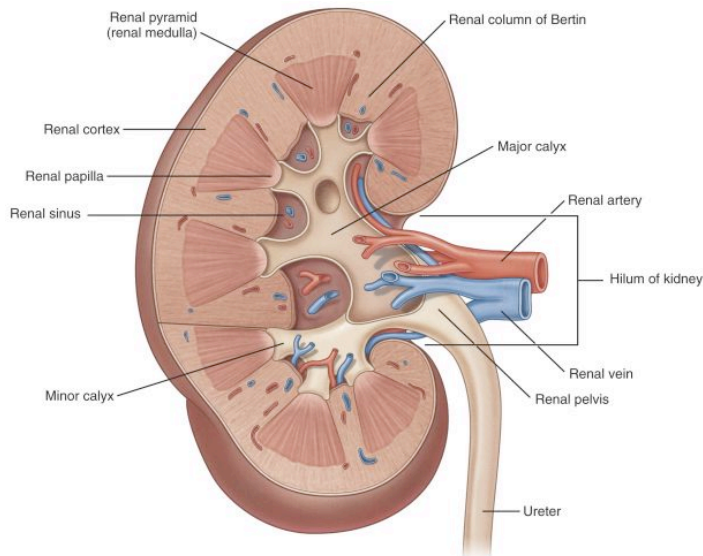
What is the blood supply to the adrenals?

- arterial → branches from inferior phrenic artery, aorta and renal artery
- venous → single vein that exits anteromedially into aorta on R and renal vein on L

What is the lymphatic drainage of the adrenals?

- follows the adrenal vein and empties into the para-aortic nodes

THE KIDNEYS



Gross and Microscopic Anatomy

What are the 8 main functions of the kidney? }} “WEB DECAF”

- 1) **W**aste excretion
- 2) **E**lectrolyte regulation
- 3) **B**P control
- 4) **D**rug metabolism
- 5) **E**po production
- 6) **C**a and **P**O₄ metabolism (1,25-dihydroxyVit D)
- 7) **A**cid-base regulation
- 8) **F**luid homeostasis

What do the kidneys look like grossly?

- 150g in M, 135g in F
- 10-12cm vertically, 5-7cm transversely, and 3cm in AP
- R tends to be shorter & wider, and sits 1-2cm lower
- in kids, relatively larger with more prominent fetal lobations
- can find a Dromedary Hump → focal bulge in parenchyma along lateral contour (normal)
- renal sinus lies at medial aspect of kidney and is filled with renal sinus fat and contains vascular structures and collecting system before exiting the kidney
- composed of cortex (peripheral, lighter in colour) & medulla (distinct renal pyramids, darker in colour)
- apex of renal medulla is papilla → each papilla is cupped by a minor calyx

Describe the rotational axes of the kidney

- 30° anterior rotation, medial tilt of upper poles, anterior displacement of lower pole

What are the columns of Bertin?

- extensions of renal cortex found between the renal medullary pyramids
- contain renal vessels perforating to periphery from renal sinus (interlobar arteries)
 - avoided during PCNL to decrease blood loss
 - puncture into collecting system through renal medullary pyramid into calyx

Relations and Investing Fascia

Where are the kidneys located in relation to the spinal column?

- L → body of T12 to top of L3
- R → top of L1 to bottom of L3

What are the structures surrounding the kidney?

- posteriorly (upper 1/3rd) → diaphragm
- medially (lower 2/3rds) → psoas
- laterally → quadratus lumborum and aponeurosis of transversus abdominis muscle
- right kidney } hepatorenal ligament → extension of parietal peritoneum
 - } upper pole → adrenal
 - } medial of right (upper 1/3rd) → duodenum
 - } anteriorly → hepatic flexure of colon
- left kidney } splenorenal ligament → attaches to splenic capsule
 - } upper pole → adrenal (slightly medial), spleen, tail of pancreas, and splenic vessels
 - } anteriorly → splenic flexure of colon

Describe Gerota's fascia

- **extension off transversalis fascia (intermediate stratum)**
→ **Toldt's leaf (anterior), Zuckerkandl's leaf (posterior)**
- encloses kidney & perinephric fat } surrounded by paranephric fat
- closed superiorly & laterally } fuses with other side medially, extending across midline
 - } open potential space inferiorly

What are the boundaries of Petit's triangle?

- inferiorly → crest of ilium
 - laterally → external oblique muscle
 - medially → latissimus dorsi muscle
 - floor → internal oblique muscle
- \ / can drain psoas/retroperitoneal abscess
/ via Petit's triangle

Renal Vasculature

Describe the renal pedicle

- at level of **L2 vertebra** } vein anterior, artery posterior, renal pelvis and ureter most posterior (VAP)

Describe the arterial blood supply of the kidney * no collaterals → end arteries *****

- renal artery } gives off branches (adrenal, renal pelvis, ureter)
- segmental → most commonly;
 - 1 posterior (branches before entering hilum, so posterior to renal pelvis)
*** can cause UPJO if crosses anterior to ureter ***
 - 4 anterior (apical, upper, middle, lower/basilar → variability)
- lobar
- interlobar (run through columns of Bertin)
- arcuate (run along corticomedullary jxn)
- interlobular
- afferent (to glomerulus) → efferent to vasa recta

Describe the venous drainage of the kidney * ++ collaterals *****

- efferent arteriole to vasa recta
- interlobular (communicate freely via subcapsular plexus)
- arcuate
- interlobar
- lobar
- segmental (parallels segmental arteries } due to collaterals, can be sacrificed)
- renal vein

Where is the avascular plane of the kidney?

- between the posterior segmental & anterior segmentals } Brodel's line
- usually posterior to lateral margin } can inject dye into posterior branch to identify

How common are anatomic variations in renal vasculature?

- occurs in 25-40% of people
- **most common variation is supernumerary renal arteries (more often on L)**
 - more common to UP than LP
- less common to have supernumerary renal veins (usually on right)
- may have retroaortic left renal vein
 - can also have circum-aortic renal vein
- variations more common in ectopic kidneys, horseshoe kidneys

Renal Lymphatics

Describe the lymphatic drainage of the kidney

- lymphatics drain through columns of Bertin into renal sinus, then exit vial hilum
- branches from renal capsule, pelvis, upper ureter, perinephric tissues drain into LNs near renal vein
- the drainage then varies according to side (NO left to right);
 - right → paracaval and right interaortocaval nodes (from common iliacs to diaphragm)
 - can also go to retrocrural nodes or the para-aortic nodes
 - left → para-aortic nodes (from IMA to diaphragm)
 - can also go to retrocrural nodes or directly into thoracic duct above diaphragm

Renal Collecting System

Describe the microscopic anatomy of the collecting system

- renal corpuscle
 - in renal cortex } glomerulus (covered by podocytes) and Bowman's capsule
- PCT
- loop of Henle → extends variable lengths into medulla (descending and ascending limbs)
- DCT
- collecting tubules
- collecting duct → empties into apex of medulla, the renal papilla

Describe the gross anatomy of the collecting system

- 1) renal papilla
 - usually 7-9 per kidney } anterior (lateral) & posterior (posterior) rows
 - drains into minor calyces
- 2) minor calyces
 - have intrinsic pacemaker cells that are responsible for ureteral peristalsis
 - compound calyces more common at upper & lower poles (more prone to scarring)
- 3) infundibulum → variable diameters
- 4) major calyces → upper, middle, lower pole
- 5) renal pelvis → variable size from small intrarenal to large extrarenal
- 6) UPJ

Renal Innervation

What is the innervation of the kidney?

- autonomic → vasomotor control (although not essential eg Tx)
- sympathetics → T8 to L1 → celiac & aorticorenal ganglia → via autonomic plexus along renal artery
- parasympathetics → vagus nerve → travel with sympathetics

THE URETERS

Describe the 3 layers of the ureter

- generally 22-30cm, ~5mm in diameter
- 1) inner layer → transitional epithelium overlying lamina propria
- 2) muscle layer → smooth muscle layer contiguous with muscle covering renal calyces & renal pelvis
 - consists of **inner longitudinal & outer circular layer**; provides peristalsis
 - **3rd outer smooth muscle layer exists in distal ureter**
- 3) outer layer → adventitial layer that encompasses blood vessels & lymphatics that travel along ureter

Describe the course of the ureters?

- begins at UPJ, which lies posterior to renal artery
- travels inferiorly along anterior surface of psoas muscle
- 1/3 of way to bladder, the ureter crosses under the gonadal vessels then crosses over the iliac vessels, generally marking the bifurcation of common iliacs into internal & external
- in F pelvis, the ureter is **crossed anteriorly by the uterine artery** & is closely related to cervix
 - **common locations for ureteric injury during gyne OR**
- head toward bladder underneath obliterated umbilical artery (branch of internal iliac)

List structures that cross over the ureter in the female

- gonadal vein
- round ligament
- obliterated umbilical artery
- uterine artery
- superior vesical artery
- inferior vesical artery

What are the 3 narrowest parts of the ureter?

- 1) UPJ
- 2) crossing over the iliac vessels
- 3) UVJ → **narrowest part**

Describe the ureteral segments

- 1) abdominal ureter (UPJ to iliacs) and pelvic ureter (iliacs to UVJ)
- 2) upper (UPJ to upper border of sacrum), middle (upper to lower border of sacrum) & lower (lower border of sacrum to bladder)

What is the blood supply to the ureters?

- arterial supply from multiple branches along its course (venous follows arterial)
- **MEDIAL supply to abdominal ureter & LATERAL supply to pelvic ureter**
- upper → renal artery, gonadal artery, aorta, common iliac artery
- lower → internal iliac artery or its branches (vesical, uterine, middle rectal, vaginal arteries)
- ureteric arterial vessels travel longitudinally within periureteral adventitia

What is the lymphatic drainage of the ureters?

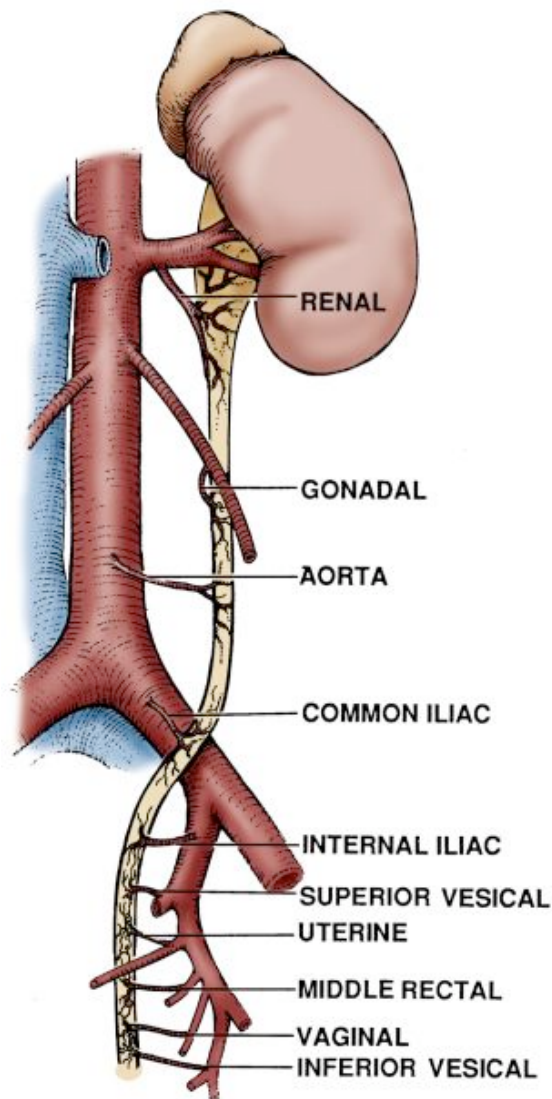
- abdominal → para-aortic for L ureter; right paracaval & inter-aortocaval nodes for R
- pelvic → internal, external & common iliac nodes
- upper & renal pelvis → joins renal lymphatics

What is the innervation of the ureter?

- **peristalsis doesn't need outside autonomic input**
- peristalsis originates & propagates from intrinsic smooth muscle pacemaker sites in **minor calyces**
- ureter does get some autonomic input (likely a modulating effect) but the role is unclear;
- sympathetics } some preganglionic fibers from T10-L2
 } some postganglionic fibers from ganglia in aorticorenal, superior & inferior hypogastric autonomic plexuses
- parasympathetics } S2-S4

Why does renal colic occur?

- renal pain fibers stimulated by distention in renal capsule, renal collecting system, or ureter
→ mediated by PGs } role of NSAIDs in management of renal colic
- direct mucosal irritation may also stimulate nociceptors
- signals travel with the sympathetics and result in a visceral-type pain
→ can get N/V



→ ARTERIAL BLOOD SUPPLY TO THE URETER

Chapter #2 – Anatomy of the Lower Urinary Tract and Male Genitalia

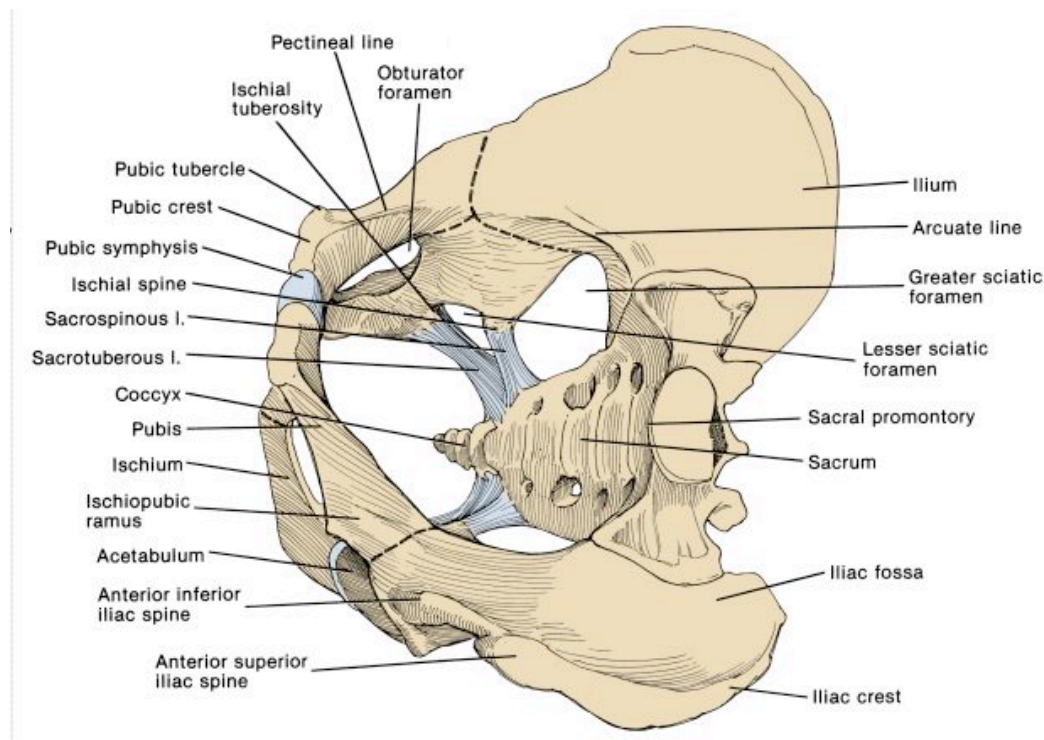
BONY PELVIS

What are the bones of the pelvis?

- 1) sacrum
- 2) ilium
- 3) ischium
- 4) acetabulum

What are the palpable landmarks of the bony pelvis?

- ASIS
- PSIS
- iliac crest
- pubic tubercles
- ischial tuberosities



What is the difference between the true and false pelvis?

- true → contents below arcuate line (sacral promontory to pectineal-line)
- false → formed by the iliac fossae and largely in contact with intraperitoneal contents

What structures give strength to the SI joint?

- sacrospinous ligament → ischial spine to sacrum (separates greater and lesser sciatic foramen)
- sacrotuberous ligament → ischial tuberosity to sacrum
- anterior and posterior ligaments

ANTERIOR ABDOMINAL WALL

Skin and Subcutaneous Fasciae

List the different layers of the abdominal wall.

- skin
- Camper's fascia → loose layer of fatty tissue that has vessels (eg superficial inferior epigastric vessels encountered during inguinal incision)
- Scarpa's fascia → continuous with Colles' fascia of perineum and deep fascia lata of thigh
→ attaches to the clavicles superiorly
→ Colles' fascia } continuous with dartos fascia of penis & scrotum and attaches to posterior edge of UG diaphragm and to inferior ischiopubic rami
- anterior rectus sheath
- rectus abdominis muscles
- posterior rectus sheath

What keeps the perineal hematoma, associated with urethral injuries, contained?

- "butterfly hematoma"
- **must have rupture of Buck's fascia } Colles' fascia limits spread**
- laterally → fascia lata of thigh and fusion of Colles' to ischiopubic rami
- posteriorly → perineal body/membrane
- anteriorly → can travel freely under Scarpa's fascia to level of clavicles

What makes up the layers of the rectus sheath?

- above arcuate line (1/3 down from umbilicus to pubis)
 - anterior → aponeurosis of external oblique and part of internal oblique
 - posterior → aponeurosis of part of internal oblique & transversus
- below arcuate line
 - anterior → aponeurosis of external, internal & transversus abdominis
 - posterior → transversalis fascia & peritoneum

Abdominal Musculature

What are the muscles of the anterior abdominal wall?

- rectus abdominis → pubis to xyphoid and adjacent costal cartilages
→ tendinous intersections connect it to anterior rectus sheath so rectus can be divided transversely without retracting
→ supplied by T6-T12
- pyramidalis → within anterior rectus sheath from pubic crest to linea alba
→ supplied by T12

Inguinal Canal

What are the contents of the inguinal canal?

- Men → spermatic cord
→ ilioinguinal nerve (L1)
- Women → round ligament
→ ilioinguinal nerve (L1)

What are the borders of the inguinal canal?

- anterior wall & floor → external oblique aponeurosis (inguinal ligament at inferior edge)
- posterior wall → transversalis fascia
- roof → fibers of internal oblique & transversus abdominis (fuse to form conjoint tendon)

Where is the internal inguinal ring located?

- midway between ASIS and pubic tubercle
- above inguinal ligament
- 4cm lateral to external ring
- lateral to inferior epigastric vessels

What are the borders of the femoral triangle?

- superiorly → inguinal ligament
- medially → lateral border of adductor longus muscle
- laterally → medial border of sartorius muscle
- floor → adductor longus, pectineus, iliopsoas (medial to lateral)
- roof → tensor fascia lata
- contents → femoral vein, artery, nerve, femoral branch of GF nerve, lymphatics

What are the borders of the femoral canal?

- anterior → inguinal ligament (Poupart's)
- posterior → pectineal ligament (Cooper's)
- medial → lacunar ligament (Gilbert's)
- lateral → femoral vein & iliopsoas

Internal Surface of the Anterior Abdominal Wall

What are the 3 elevations of peritoneum on the internal surface of the anterior abdo wall (below umbilicus)?

- 1) median → overlies median umbilical ligament (urachus)
- 2) medial → overlies obliterated umbilical artery (originated from internal iliac, lateral to ureter)
- 3) lateral umbilical fold → contains the inferior epigastric vessels

SOFT TISSUES OF THE PELVIS

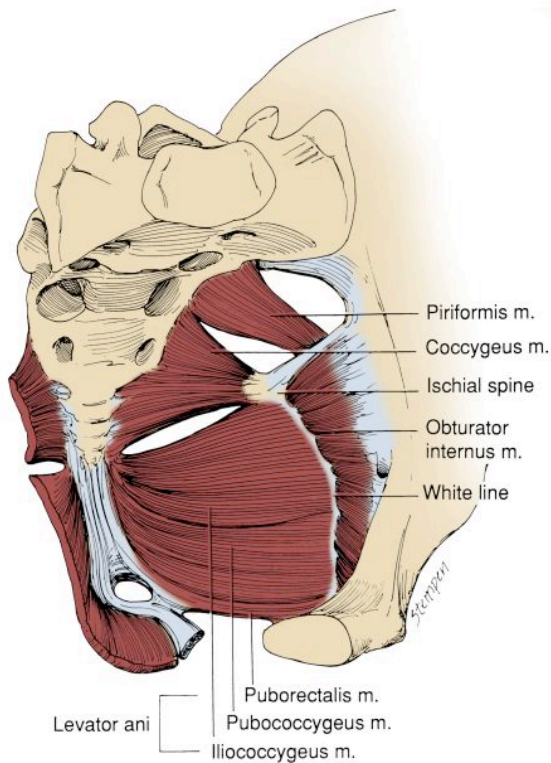
Pelvic Musculature

Name the main muscles of the pelvic diaphragm?

- 1) Obturator internus → from inner obturator foramen, through lesser sciatic foramen, to femur
→ fascia overlying this muscle forms tendinous arc that is the origin of levators
- 2) Levator ani → pelvic diaphragm muscles which contain a hiatus anteriorly
- urethra, vagina, rectum pass through UG hiatus
→ iliococcygeus \ } forms horizontal levator plate posterior to anus
→ pubococcygeus /
→ puborectalis
- 3) coccygeus → ischial spine/sacrospinous ligament to lateral border of sacrum and coccyx
- 4) piriformis → from lateral aspect of sacrum, passes through and fills greater sciatic foramen

What types of muscle are found in the pelvic diaphragm?

- type-1 → slow twitch
- type-2 → fast twitch



Pelvic Fasciae

Describe the pelvic fascia.

- contains collagen, smooth muscle & elastic tissue (so may have role in support AND function)
- continuous with retroperitoneal fascia
- contains 3 layers:
 - 1) outer → **endopelvic fascia**
 - lines inner surface of pelvic muscles
 - **continuous with transversalis fascia layer**
 - fixed to arcuate line of pelvis, Cooper's ligament, sacrospinous ligament, ischial spine, and tendinous arc of levator ani
 - 2) intermediate → embeds pelvic viscera in a fatty, compressible layer that is easily swept away to expose deeper potential spaces
 - contains all pelvic vessels and some pelvic nerves
 - 3) inner → lies just beneath peritoneum, covering rectum & dome of bladder, to form Denonvilliers' fascia

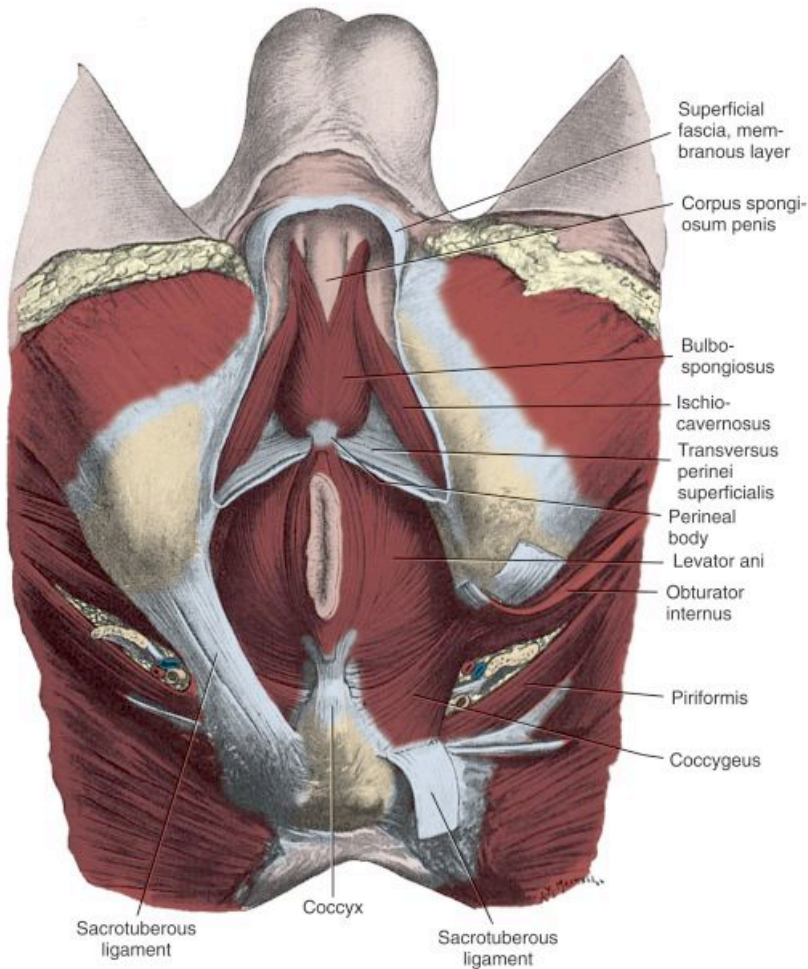
What are the 3 most important components of the pelvic fascia?

- 1) anteriorly → **puboprostatic ligaments** → attaches to lower 5th of pubis, lateral to symphysis and to jxn of prostate and external sphincter
 - pubourethral ligaments in women → insert on proximal 3rd of urethra
- 2) laterally → **arcus tendineus fascia pelvis** (ATFP) extends from puboprostatics (pubourethrals) to ischial spine
 - forms at jxn of endopelvic and visceral fascia
 - significant in SUI, urethroceles, cystoceles
- 3) posteriorly → fans out laterally from rectum to pelvic side wall as **lateral & posterior vesical ligaments**
 - cardinal & uterosacral ligaments in women

Fasciae of the Perineum and the Perineal Body

Where is the weakest point in the pelvic floor?

- urogenital hiatus



Describe the UG diaphragm.

- triangular in shape; from pubis to ischial tuberosities
- perineal membrane lies at center of UG diaphragm and defines it
- ends abruptly posteriorly w/ superficial & deep transverse perinei running along its free edge
- external genitalia attach to its inferior surface
- superiorly it supports urethral sphincter
- perineal body represents point of fusion b/w free edge of UG diaphragm & posterior apex of UG hiatus

Which muscles insert into the perineal body?

- pyramid-shaped structure is the key to pelvic support
- almost every pelvic muscle inserts into perineal body (6) } } } "TREBLE"
 - **superficial & deep Transverse perinei**
 - **Rectourethralis**
 - **EUS**
 - **Bulbospongiosus**
 - **Levator ani**
 - **External anal sphincter**
- most pelvic fascia also insert into the perineal body (4)
 - **perineal membrane**
 - **Colles'**
 - **Denonvilliers'**
 - **endopelvic fascia**

PELVIC CIRCULATION

Arterial Supply

What are the branches of the Internal iliac artery (aka hypogastric)?

- **POSTERIOR branch (3) }** **“pALS”**
 - 1) Ascending lumbar → supplies posterior abdo wall (psoas, quadratus lumborum)
 - 2) Lateral sacral → passes medial to meet up with middle sacral from aorta
 - 3) Superior gluteal → exits via greater sciatic foramen
- **ANTERIOR branch (8) }** **“OSIOMUII”**
 - 1) Obliterated umbilical
 - 2) Superior vesical → from proximal portion of obliterated umbilical to bladder, ureter, SV
 - 3) Inferior vesical → bladder base, lower ureter, prostate and SVs (vagina)
 - gives off **vesiculodeferential branch** to the SVs and vas deferens
 - 4) Obturator → medial and inferior to obturator nerve and supplies adductors of thigh
 - 5) Middle rectal → meets up with superior & inferior rectals but also gives off branches to rectum, bladder, prostate and SVs
 - 6) Uterine → passes above & anterior to ureter to ascend lateral wall of uterus to meet ovarian artery
 - 7) Inferior gluteal → travels via greater sciatic foramen to supply buttock and thigh
 - 8) Internal pudendal (terminal branch) → leaves pelvic cavity into perineum via greater sciatic foramen and ends as common penile
 - supplies rectum, perineum, external genitalia

What are the branches of the Internal pudendal artery (terminal branch of internal iliac)?

- IPP BP/CP
- 1) **I**nferior rectal artery
- 2) **P**erineal artery
- 3) **P**osterior scrotal (posterior labial)
- 4) artery of **B**ulb of **P**enis
- 5) **C**ommon **P**enile artery (terminal branch) → dorsal + cavernosal + bulbourethral

What are the branches of the External iliac artery? *** runs anterior and lateral to veins ***

- 1) inferior epigastric → medial to internal inguinal ring
 - gives off **deep circumflex branch** laterally & **pubic branch** medially
 - also gives off **cremasteric branch & external pudendal branch**
 - **25% have accessory obturator artery (runs medial to femoral vein)**
- 2) femoral artery

Venous Supply

What is the drainage of the dorsal venous complex?

- dorsal vein of penis passes between inferior pubic arch and external sphincter to reach pelvis
 - trifurcates into central superficial branch + 2 lateral plexuses
- 1) **superficial branch** } pierces endopelvis fascia between puboprostatics and drains retropubic fat, anterior bladder and anterior prostate
- 2) **lateral plexuses x2** } sweep on lateral surface of prostate, draining it and the rectum;
 - it then communicates with **vesical plexuses** on lower part of bladder
- 3-5 inferior vesical veins emerge from these lateral vesical plexuses; drains into Int iliac vein

*** in females, dorsal clitoral vein bifurcates to empty into lateral vaginal plexuses; these connect w/ vesical, uterine, ovarian, and rectal plexuses to drain into the Int iliac vein ***

*** connections exist between pelvic plexuses and emissary veins of pelvic bones and vertebral plexuses; proposed route for dissemination of pelvic processes to pelvic & axial bone ***

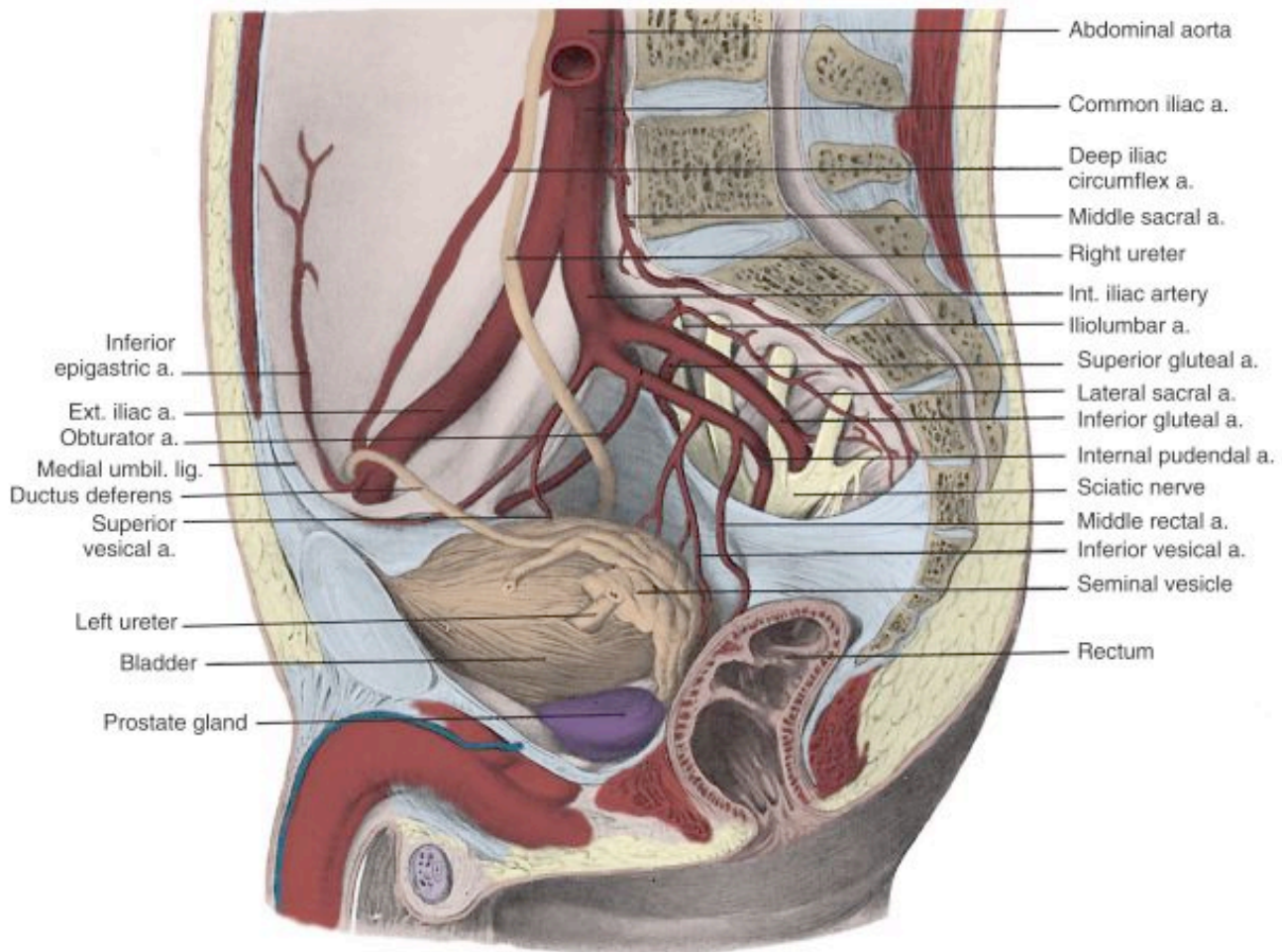
What is the drainage of the external & internal iliac veins?

- both are found medial and posterior to respective arteries
- join to form common iliac behind internal iliac artery
- **50% of patients have an accessory obturator vein that drains into the underside of the external iliac vein (can be torn doing pelvic LN dissection)**

Pelvic Lymphatics

What are the 3 major lymph node groups of the pelvis?

- 1) Internal iliac nodes → tributaries include presacral, obturator, and internal pudendal nodes
- 2) External iliac nodes → lateral, anterior, and medial to vessels
→ drains anterior abdo wall, urachus, bladder, and internal genitalia
- 3) superficial & deep inguinal nodes → drains perineum and external genitalia



PELVIC INNERVATION

Lumbosacral Plexus

Describe the somatic nerves of the lumbosacral plexus (CHART)?

- 1) Iliohypogastric (L1)
 - *motor* to internal oblique & transverses; *sensory* to posterolateral gluteal skin
 - travels b/w internal oblique and transversus, then pierces internal & external oblique about 3cm above external inguinal ring
- 2) Ilioinguinal (L1)
 - *motor* to internal oblique & transversus; *sensory* to upper medial thigh & base of penis/mons
 - passes through internal oblique, enters inguinal canal laterally, and travels anterior to spermatic cord
 - can be damaged during radical orchidectomy } numbness to anterior scrotum & medial thigh
- 3) **Lateral Femoral Cutaneous nerve of thigh** (L2-L3)
 - *sensory* to anterior and lateral thigh to knee
 - seen lateral to psoas muscle in iliacus fascia
- 4) **Genitofemoral** (L1-L2)
 - *motor* to cremaster & dartos muscles in scrotum (genital branch only); *sensory* to scrotum, mons, labia majora & skin of upper thigh (genital & femoral branches)
 - lies directly atop and parallels psoas
- 5) **Femoral** (L2-L4)
 - *motor* to psoas, iliacus & large muscles of ant. thigh (quads); *sensory* to ant. thigh & medial leg
 - hidden within psoas until it exits abdomen just lateral to femoral artery
 - can be injured during psoas hitch or by retractor placed on inguinal ligament (can't extend knee + numb on anterior thigh)
- 6) **Obturator** (L2-L4)
 - *motor* to adductor thigh muscles (longus, brevis, gracilis, pectineus); *sensory* to medial thigh
 - emerges into pelvis from beneath psoas, lateral to internal iliac vessels, passing into obturator canal via the obturator foramen
 - can be injured during RP pelvic LN dissection (can't adduct leg)
- 7) lumbosacral trunk (L4-L5)
 - passes into pelvis behind psoas & joins sacral nerves to form sacral plexus
 - sacral plexus lies on pelvic surface of piriformis deep to endopelvic fascia & posterior to internal iliac vessels
 - leaves pelvis via greater sciatic foramen just posterior to sacrospinous ligament
 - can be injured during sacrospinous culposuspension & with exaggerated lithotomy there may be pressure placed on its peroneal branch at the fibular head causing footdrop
- 8) Sciatic (L4-S3)
 - **body's largest nerve**
 - *motor* and *sensory* to legs (common peroneal + tibial)
- 9) Pudendal (S2-S4)
 - branches include inferior rectal nerves, dorsal penile nerve, perineal nerve

What are the pelvic & perineal branches of the sacral plexus?

- 1) posterior femoral cutaneous (S2-S3) → *sensation* to perineum, posterior scrotum and thigh
- 2) pudendal (S2-S4) → *motor* to levators, UG diaphragm, anal sphincter, and EUS
→ *sensation* to perineum, scrotum, penis, urethra
- 3) nervi erigentes (S2-S4) → parasympathetics
- 4) pelvic somatic efferent nerves (S2-S4) → *motor* to levators and EUS

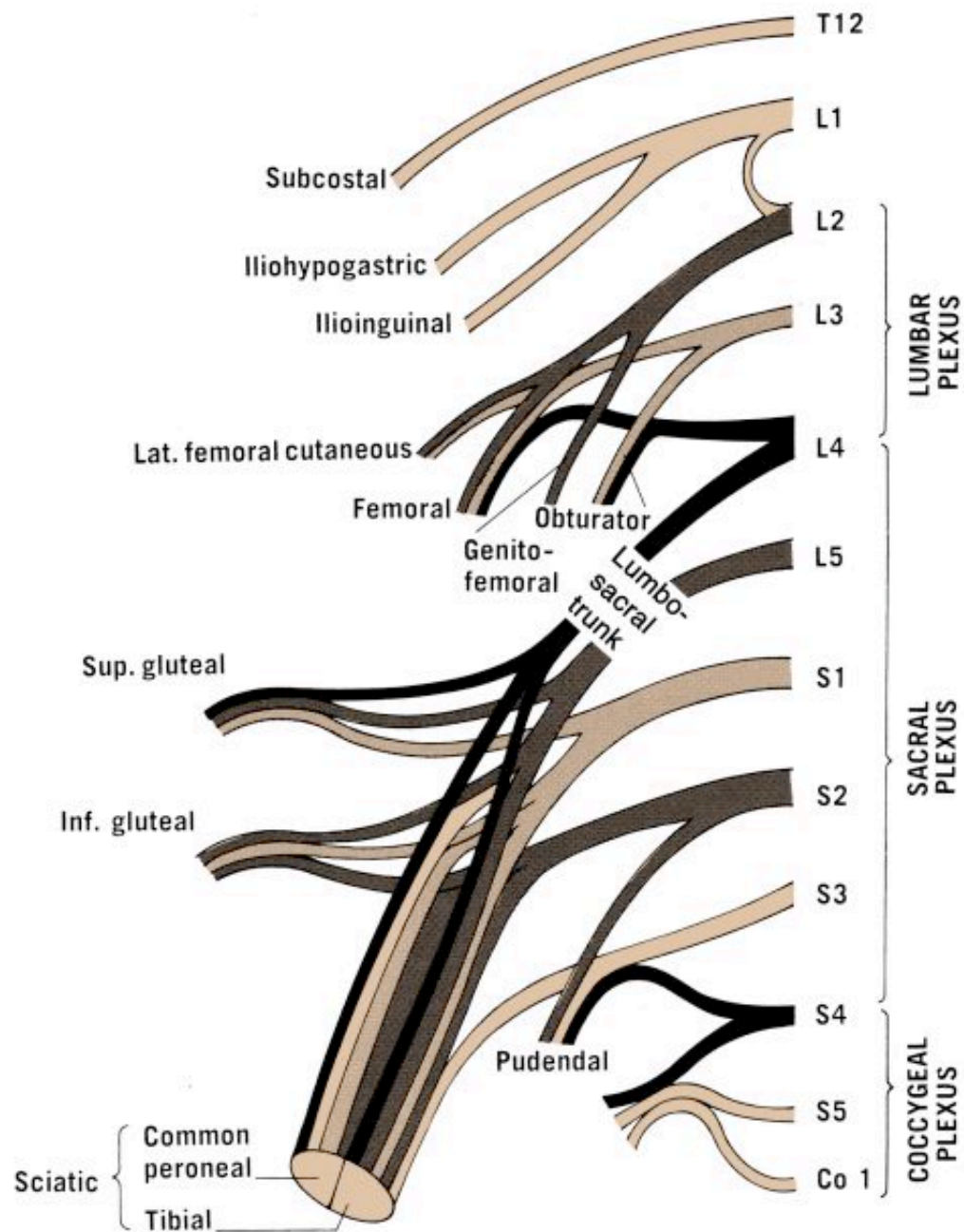
What are the branches of the pudendal nerve?

- | | | |
|---|---|--|
| 1) inferior rectal nerves (first branch) | } | pudendal nerve exits pelvis via greater sciatic foramen & enters perineum via lesser sciatic foramen, then traveling through Alcock's canal |
| 2) dorsal nerve of penis/clitoris | | |
| 3) perineal nerve (gives off posterior scrotal) | / | |

List nerves (and their nerve roots) of the LUMBAR PLEXUS.

→ "GOLF"

- lateral femoral cutaneous nerve (L2-3)
- femoral nerve (L2-4)
- genitofemoral nerve (L2) } genital branch, femoral branch
- obturator nerve (L3-4)



→ LUMBOSACRAL TRUNK

Pelvis Autonomic Plexus

Describe the pelvic (inferior hypogastric) autonomic plexus

- sympathetic & parasympathetics
- rectangular and 4-5cm long
- midpoint is at tips of SVs
- sits on either side of rectum and is pierced by vessels going to & from rectum, bladder, SVs & prostate
- can be damaged during the division of the lateral pedicles of the bladder and prostate
- nerve branches follow the pelvic blood vessels
- **most caudal portion of pelvic plexus gives rise to the all important cavernosal nerves**
 - cavernosal nerves pass tips of SV then lie in leaves of the lateral endopelvic fascia, traveling on posterolateral aspect of prostate
 - these nerves are most vulnerable at apex of prostate (found at 5- and 7-o'clock)

How do preganglionic fibers get to the pelvic autonomic plexus?

- **sympathetics** → **T10-L2** lateral column of grey matter (sympathetic chain)
 - reach inferior hypogastric (pelvic) plexus via;
 - 1) **superior hypogastric plexus** → celiac + first 4 lumbar splanchnics
 - anterior to aortic bifurcation then enters pelvis after bifurcating
 - responsible for ejaculation
 - 2) branches from pelvic continuations of the sympathetic trunks that have fused deep in front of coccyx
- **parasympathetics** → **S2-S4** intermediolateral column (nervi erigentes/pelvic splanchnics)
 - **join hypogastric nerves and branches from sacral sympathetics to form inferior hypogastric (pelvic) plexus**

PELVIC VISCERA

Rectum

Describe the location of the rectum

- begins around level of S3 where sigmoid mesentery disappears
- peritoneum covers anterior upper 2/3 of rectum (pouch of Douglas) down to SVs or posterior vaginal fornix
- separated from bladder and prostate down to the level of the EUS by Denonvillier's fascia
- rectal wall is composed of inner layer of circular smooth muscle and a continuous sheet of outer longitudinal smooth muscle (from tenia of colon)
- dilates to form rectal ampulla before exiting via the anal canal
- anterior fibers of outer longitudinal smooth muscles of colon leave rectum to join posterior EUS forming the **rectourethralis muscle**
- ampulla of rectum is in close proximity to apex of prostate and can be injured during RP

What is the blood supply to the rectum?

- 1) superior rectal artery → from IMA
- 2) middle rectal artery → from internal iliac artery
- 3) inferior rectal artery → from internal pudendal (branch of internal iliac)

Pelvic Ureter

Describe the course of the pelvic ureters

- they are ~5cm apart when they cross the iliacs (narrowest point)
- diverge widely along pelvic side wall towards ischial spines & travel on anterior surface of int. iliacs
- crosses back medially near ischial spine
- in M, crossed anteriorly by vas, then runs with the inferior vesical artery/vein to the bladder
- in F, ureter runs posterior to ovary then turns medially, running deep to base of broad ligament
→ crossed anteriorly by uterine a. then travels 1-4cm on ant. vaginal wall to bladder

Where does the ovarian vessel lie in relation to the pelvic ureter?

- crosses the iliac vessels **anterior & lateral to the ureter** ; injury during dissection possible

What is the blood supply to the pelvic ureter?

- **enters laterally**, so dissection should only be medial
- gets blood supply from common iliac, most branches of internal iliac, inferior vesical, uterine
- intramural vessels of the ureter run within adventitia
 - 75% have longitudinal vessels running the length of the ureter w/ anastomosing segmental ureteral vessels
 - 25% have fine interconnecting plexuses with less collateral flow (higher risk of ischemic injury) → more common to have this form in pelvic/distal ureter

What is the lymphatic drainage of the pelvic ureter?

- external, internal and common iliac nodes

List 5 structures divided in order to access the distal ureter in a female.

- round ligament
- obliterated umbilical artery
- uterine artery
- superior vesical artery
- inferior vesical artery

Bladder

Describe the urachus.

- anchors bladder to anterior abdo wall
- bladder wall is thin at point of attachment of urachus; can get diverticulae
- composed of longitudinal smooth muscle bundles derived from bladder wall; fibrous close to umbilicus and fuses with one of obliterated umbilical arteries
- usually has an epithelium-lined lumen that persists; can give rise to nasty urachal adenoCa, umbilical urinary fistulae, etc

Describe the space of Retzius.

- potential space antero-inferior & lateral to bladder
- perivesical/retropubic fat and loose connective tissue cushions bladder from pelvic sidewall

Describe the location of the bladder neck

- found 3-4cm behind midpoint of pubic symphysis
- firmly fixed here by endopelvic fascia and by its continuity with the prostate
- in infants, bladder is level with upper border of the symphysis } sits much higher in infants

What are the layers of the bladder wall?

- transitional epithelium → 6 cells thick and sits on BM
- lamina propria → thick layer of fibroelastic connective tissue
→ contains blood vessels and smooth muscle fibers (muscularis mucosa)
- muscularis propria → arranged into **inner longitudinal, middle circular, outer longitudinal** layers (clearly separated at bladder neck, undiscernable at dome)

Describe the male & female bladder neck musculature.

- M → inner longitudinal fibers pass through to become inner longitudinal layer of smooth muscle in urethra
 - middle circular layer forms a circular preprostatic sphincter (BN continence) that is richly innervated by adrenergic fibers (sympathetics)
 - outer longitudinal fibers well developed only on posterior aspect of bladder base to provide a strong trigonal backing
- F → inner longitudinal fibers converge radially to pass down as inner longitudinal layer of urethra
 - poorly developed, if not non-existent, middle and outer layers
 - very little adrenergic innervation of bladder neck with limited sphincteric fxn

Describe the UVJ.

- spirally oriented smooth muscle of ureter becomes longitudinal as it approaches bladder
- fibromuscular sheath of Waldeyer extends over the ureter 2-3cm from the bladder and follows it to the trigone (persistent Waldeyer sheath thought to be responsible for ureterocele)
- intramural portion of the ureter is 1.5 to 2cm and is considerably narrowed
- with bladder filling, there is passive occlusion of the ureter

What is the proposed mechanism of VUR?

- poor detrusor backing & insufficient submucosal ureteral length (Paquin's 5:1 ratio)

What is a Hutch diverticulum?

- **herniation of bladder wall at weakest point of detrusor hiatus, above ureter**
- thought to be from chronically elevated intravesical pressures, which can also cause VUR

Describe the trigone of the bladder.

- triangle of smooth muscle between ureteric orifices and the internal urethral meatus
- contain fibers of longitudinal smooth muscle from ureter which are thickened along the interureteric ridge (Mercier's bar) and between the ureters and the meatus (Bell's muscle)
- muscle of trigone forms 3 distinct layers;
 - 1) superficial layer → from longitudinal inner muscle of ureter
 - extends down male urethra to insert at verumontanum
 - 2) deep layer → continuation of Waldeyer's sheath that inserts at bladder neck
 - 3) detrusor layer → outer longitudinal and middle circular smooth muscle layers of bladder wall

What is the blood supply of the bladder?

- superior & inferior vesical arteries (anterior branch of internal iliac)
- can also receive blood from any adjacent branch of internal iliac
- lateral and posterior pedicles } lateral & posterior vesical ligaments in M
 - } cardinal & uterosacral ligaments in F
- veins drain into internal iliac

What is the lymphatic drainage of the bladder?

- **mostly to external iliac nodes**
- some to internal iliac and obturator nodes, and some even to common iliac nodes

What is the innervation of the bladder?

- **autonomic afferent fibers pass from pelvic plexus**, via lateral & posterior pedicles, to bladder
 - **parasympathetics travel via cardinal ligament in F**
- bladder wall is richly supplied with parasympathetic cholinergic receptors (M2 >> M3) but has very little sympathetic adrenergic receptors
 - **M3 is more clinically relevant**
- a special nonadrenergic, noncholinergic (NANC) component participates in bladder activity but the neurotransmitter hasn't been identified
- male BN is richly supplied with sympathetic α -adrenergic receptors
- efferent fibers travel via hypogastric nerves AND via parasympathetics to the T and S levels

Prostate

Describe the normal average prostate

- 20-25g
- 3cm long, 4cm wide, 2cm deep
- closed by a 'capsule' of collagen, elastin and smooth muscle → debatable!!!
- fixed to pubic bone anteriorly by puboprostatic ligaments found near apex
- cradled by levators (pubococcygeus) laterally & is directly related to overlying endopelvic fascia
 - superficial branch of dorsal vein lies outside this fascia, dorsal vein complex deep to it
- arcus tendineus fascia pelvis lies just lateral to prostate, under endopelvic fascia and close to lateral divisions of dorsal vein complex → so cut endopelvic fascia lateral to this fascia
- no true capsule at apex → can make margin status on RP path difficult to interpret

What is the composition of the prostate?

- **70% glandular** & **30% fibromuscular stroma** (collagen & smooth muscle)
- urethra runs closer to anterior surface and is lined with transitional epithelium, which can extend into prostatic ducts → need to Bx for persistently +ve cytology
- urethral crest runs from bladder down to verumontanum along posterior midline of urethra
- slit-like orifice of prostatic utricle (Mullerian remnant) is found at apex of the verumontanum
- ejaculatory ducts (covered by smooth muscle) open on either side of the utricular orifice and run ~2cm within the prostate, originating at the jxn of the SV and vas

Describe the glands of the prostate.

- tubuloalveolar glands lined with simple cuboidal or columnar epithelium
- flattened basal cells line each acinus beneath epithelial cells (?stem cells for secretory epithelium)

What are the 3 main zones of the prostate?

- 1) TZ → 5-10% of gland
 - separated from rest of gland by fibromuscular band of tissue (surgical capsule)
 - commonly gives rise to BPH, accounts for only **~20% of PCa**
- 2) central zone → 25% of gland
 - distinct from the rest of the gland (**Wolffian in origin**)
 - accounts for only **1-5% of PCa**
- 3) peripheral zone → makes up 75% of gland, covering posterolateral aspect
 - accounts for **70% of PCa**
 - ? zone most affected by chronic prostatitis

*** clinical division of lateral lobes, midline sulcus & median lobe don't correspond to any histological division ***

What is the vascular supply to the prostate?

- **prostatic artery (branch of inferior vesical artery)**
 - 1) **urethral artery** } enters prostatovesical jxn posterolaterally & supplies TZ, prostatic urethra & periurethral glands
 - largest branches enter at 4- and 8-o'clock
 - 2) **capsular artery** } run posterolateral to prostate w/ cavernous nerves in NVB
 - } pierces gland at right angles & end at pelvic diaphragm
 - } send several small branches to anterior capsule
- venous drainage is abundant through the periprostatic plexus (Santorini's)

What is the lymphatic drainage of the prostate?

- primarily to the obturator & internal iliac nodes

What is the nerve supply to the prostate?

- sympathetic & parasympathetics from the pelvic plexus travel via the cavernous nerves
 - branches follow the capsular artery
 - parasympathetics promote secretion
 - sympathetics promote contraction of smooth muscle

Membranous Urethra

Describe the membranous urethra and the EUS?

- averages 2 to 2.5cm from the apex of the prostate to the perineal membrane
- covered by the EUS → distally, forms omega shape as it fans out laterally over perineal membrane
 - posterior portion inserts into perineal body all along its length
 - innervated by **pudendal nerve** and a **branch of the sacral plexus** that runs on the surface of the levators
- membranous urethra is 'suspended' from pubis by connective tissue that inserts into puboprostatic ligament and suspensory ligament of the penis

What factors make the membranous urethra the location of highest closing pressure?

- 1) pseudostratified columnar epithelium helps to occlude lumen
- 2) submucosa is rich in blood vessels & soft connective tissue that helps with sealing
- 3) longitudinal & circular urethral smooth muscle (intrinsic component of EUS)
- 4) EUS
- 5) pubourethral component of levators

Vas Deferens and Seminal Vesicle

Describe the course of the Vas.

- covered by thick wall of outer longitudinal & inner circular smooth muscle
- lined by pseudostratified columnar epithelium
- arises from tail of epididymis and is tortuous for first 2-3cm
- travels along **posterior aspect of spermatic cord** until leaving the testicular vessels at the internal inguinal ring (lateral to inferior epigastrics)
- moves medial towards base of prostate and forms dilated ampulla where it can store spermatozoa

Describe the seminal vesicles.

- lateral outpouching of the vas
- approx 1.5cm x 5cm with a capacity of 3-4mL
- doesn't store sperm but seminal fluid (**major contributor to volume of ejaculate – 70%**)
- covered by a thin layer of smooth muscle
- lined by columnar epithelium with goblet cells
- **contributes fructose to ejaculum**

Describe the relation of the ureter to the vas and SV

- ampulla of vas is medial, SV lies lateral
- ureter enters bladder medial to tip of SV
- Denonvillier's fascia separates SV and vas from rectum

What is the blood supply to the vas and SV?

- **vesiculodeferential artery supplies both → br. of inferior vesical (br. of internal iliac)**
- may get more blood supply from superior vesical artery (also a br of internal iliac)
- both drain into the **pelvic venous plexus**

What is the lymphatic drainage of the vas and SV?

- external & internal iliac nodes

What is the innervation of the vas and SV?

- mostly from the pelvic autonomic plexus
- mainly excitatory sympathetics from hypogastric nerves } ejaculation is sympathetic

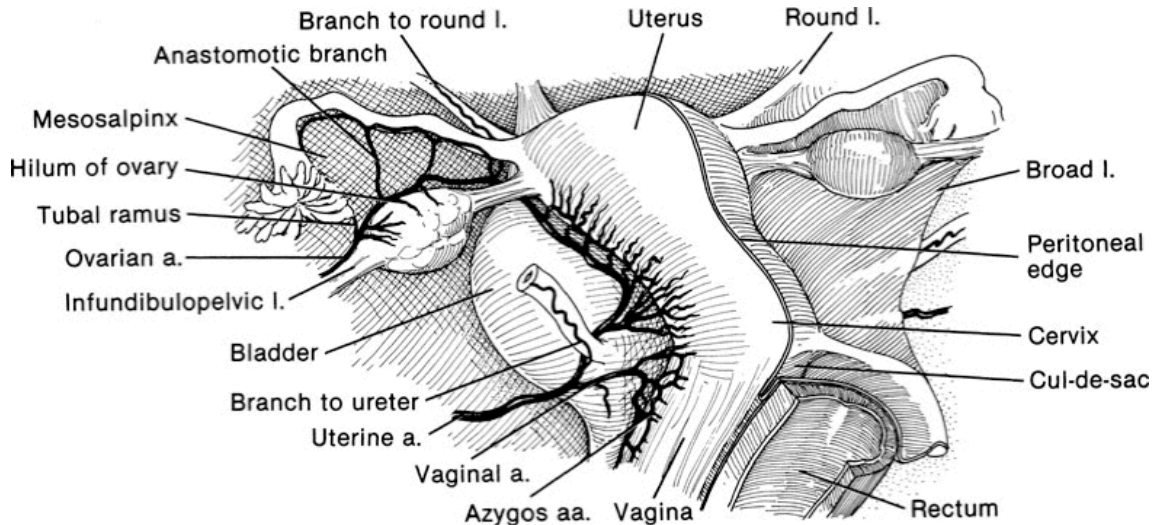
Female Pelvic Viscera

Describe the uterus

- 8x6x4cm in avg woman and lies in front of rectum and over dome of bladder
- cervix opens through anterior wall
- fallopian tubes extend laterally from jxn of corpus and fundus and is draped by broad ligament
 - four segments of fallopian tube } uterine, isthmus, ampulla, infundibulum
- ovary is held in place by mesovarium & broad ligament
- round ligament of uterus passes laterally and exits via internal inguinal ring (attaches to labial fat pad)

Where is the ureter in relation to the female pelvic organs?

- ureter can be found directly posterior to ovary, covered by pelvic peritoneum
- **uterine artery crosses anterior to ureter** and runs in broad and cardinal ligaments to supply proximal vagina, uterus, and medial 2/3 of fallopian tubes
- base of bladder lies directly in front of cervix on anterior vaginal wall
 - smooth muscle fibers tether posterior bladder wall and base to uterine cervix & vagina
- ureter travels for a short time on anterolateral aspect of proximal vaginal wall



Female Urethra

Describe the female urethra.

- on avg 4cm from bladder neck to vaginal vestibule
- lining changes from transitional to nonkeratinized squamous
- many small mucous glands open into urethra
- a group of mucous glands (Skene's glands) on either side of the distal end of the urethra empty through 2 small ducts on either side of the external urethral meatus
- **thick layer of inner longitudinal smooth muscle** travels along urethra from bladder neck to meatus (**no circular smooth muscle sphincter identified**)
- EUS invests the distal 2/3 of the female urethra
 - omega shaped distally as fibers fan off laterally onto anterior vaginal wall
- urethra is suspended beneath pubis by suspensory ligament of the clitoris (anterior urethral ligament) and the pubourethral ligaments (posterior urethral ligament)
- EUS receives dual somatic innervation like in men → **pudendal & pelvic somatics**
- little sympathetics found in female urethra
- parasympathetics cholinergic fibers found throughout smooth muscle

Female Pelvic Support

Name the 3 main supportive elements that prevent the prolapse of urogenital organs

- 1) **pubovisceral & perineal muscles** → form a sphincter around the UG hiatus
→ **play the largest role in pelvic support**
→ perineal body, levators, etc
- 2) levator plate → acts as horizontal shelf beneath bladder, cervix, posterior vagina, and rectum
- 3) cardinal & uterosacral ligaments → anchor pelvic organs over levator plate

PERINEUM

What are the borders of the perineum?

- pubis
- thighs
- buttocks
- levators (superiorly)

Anal Triangle

What are the borders of the anal triangle?

- mirror opposite of UG diaphragm
- ischial spines laterally
- coccyx posteriorly

Describe the anal sphincter.

- internal → thickening of inner circular smooth muscle layer of rectum (outer longitudinal layer thins and blends with external anal sphincter)
- external → surrounds internal anal sphincter and is divided into 3 parts
 - 1) subcutaneous → attaches to perineal body by the central tendon of the perineum
 - 2) superficial → attaches to the perineal body and coccyx
 - 3) deep → blends with puborectalis sling of levators

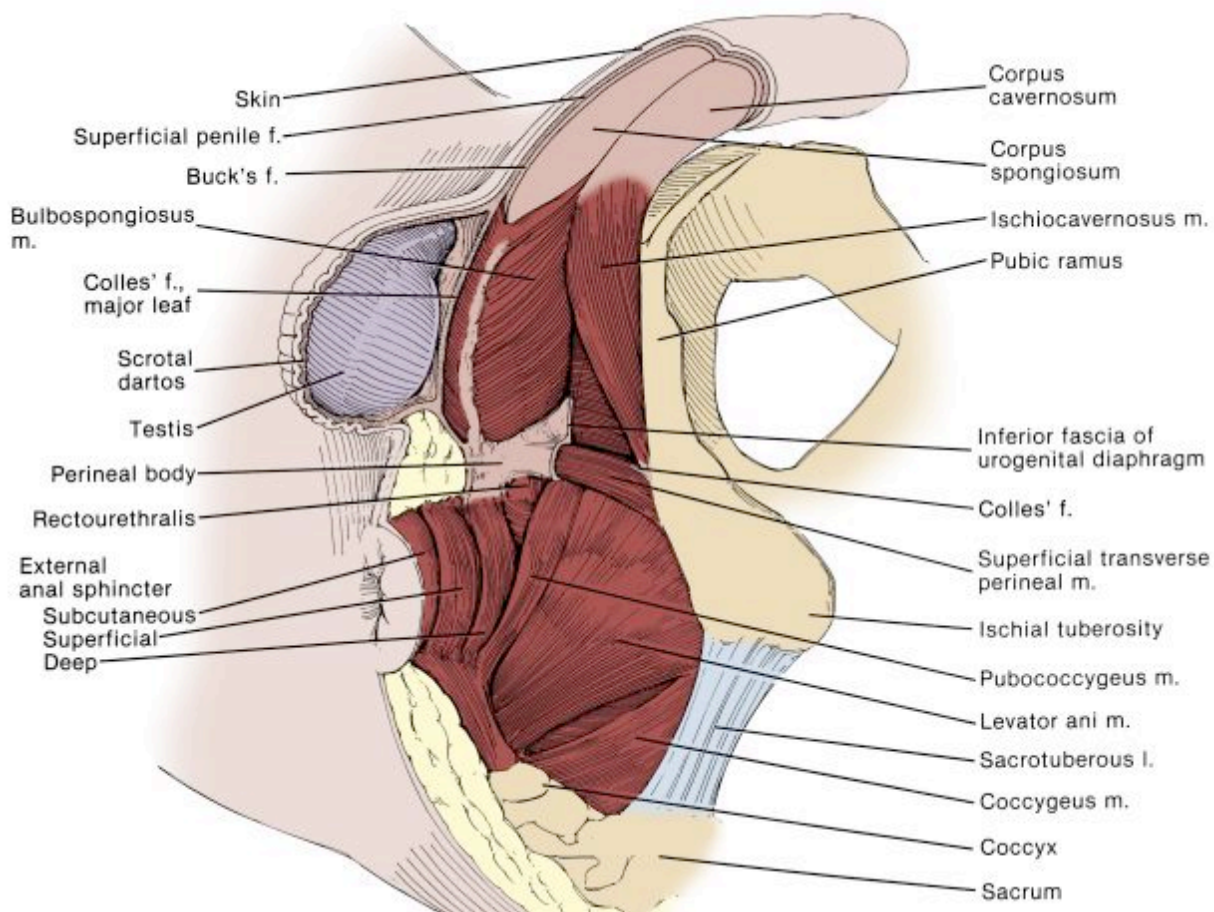
Male Urogenital Triangle

What are the borders of the UG diaphragm?

- symphysis
- ischial spines laterally
- perineal body & transverse perinei muscles (superficial and deep) make up posterior edge

Describe the contents of the superficial perineal pouch.

- superficial to UG diaphragm
- **superficial transverse perinei muscles**
- **corpora cavernosum** → attach to inferior pubic rami and perineal membrane (**crus of penis**)
→ surrounded by **ischiocavernosus muscles**
- **corpus spongiosum** → dilates as **bulb of penis** and is fixed to center of perineal membrane
→ encompassed by **bulbospongiosus muscles** (comes from perineal body)
- **bulbar urethra**
- branches of **internal pudendal vessels + pudendal nerve**
- ctx of ischiocavernosus & bulbospongiosus muscles compresses erectile bodies (potentiates erections)

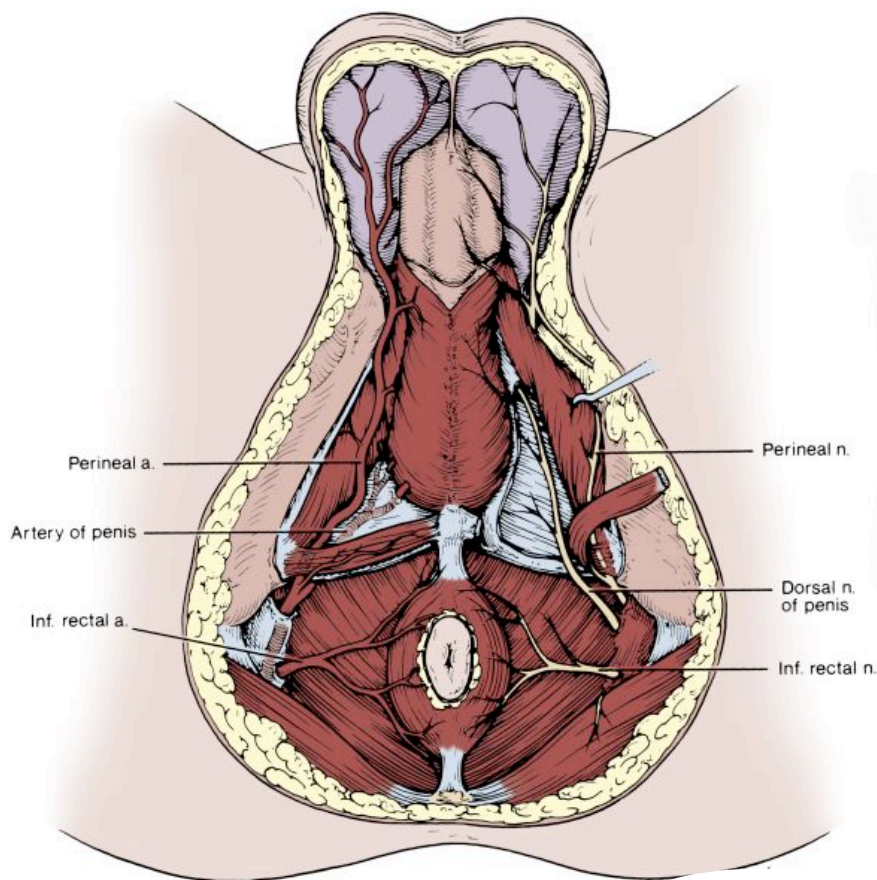


What is the blood supply to the UG diaphragm?

- mainly **internal pudendal** vessels → branch of internal iliac
 ("IPP BP/CP") → gives off a few **inferior rectal** branches then pierces Colles' to supply muscles of the superficial pouch
 - **posterior scrotal**
 - **perineal**
 - **artery to bulb of penis**
 - **common penile** (terminal branch of internal pudendal)
- internal pudendal veins communicate freely with the dorsal vein complex by piercing levators
 → these can bleed during apical dissection of prostate

What is the innervation of the UG diaphragm?

- **pudendal nerve** } comes out Alcock's canal and gives off branches
 - a) **inferior rectal branches** innervate sphincter (1st branch)
 - b) **dorsal nerve of penis**
 - c) **perineal branches** supply ischiocavernosus, bulbospongiosus, & transverse perinei as well as the EUS and levator
 → gives off posterior scrotal nerve branches



→ MALE PERINEUM

Penis

Describe the gross anatomy of the penis

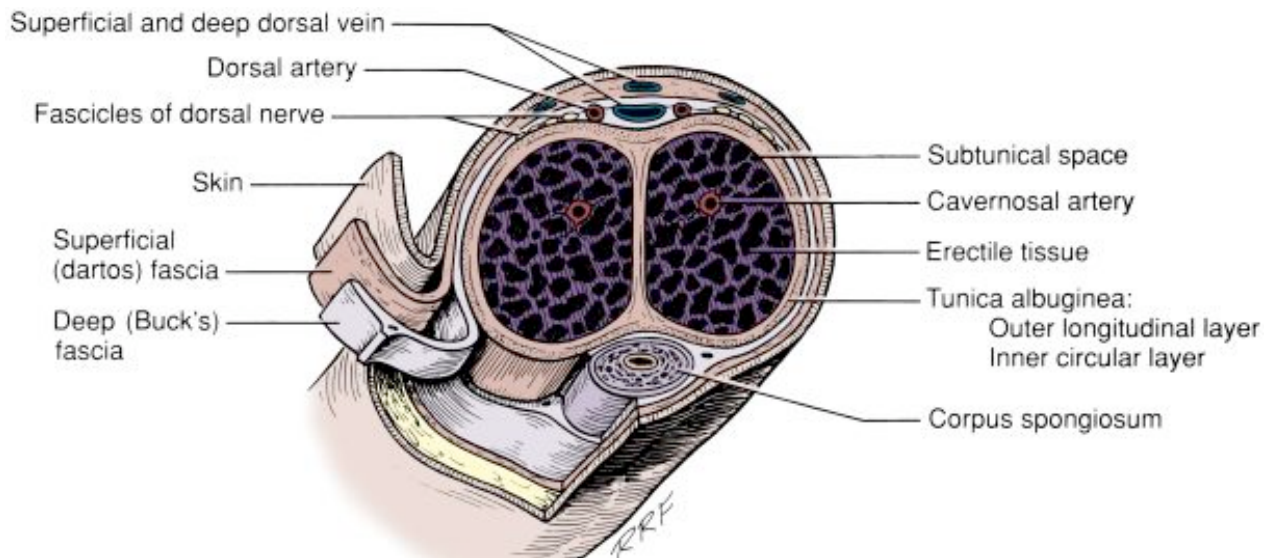
- corpora cavernosum join beneath pubis to form body of penis
 - incomplete septum distally
 - enclosed by tunica albuginea (outer longitudinal & inner circular fibers)
 - smooth muscle bundles w/in
- distal to bulb, corpus spongiosum tapers and runs on ventral surface of cavernosa, then expands to form glans
 - urethra runs along entire length, starting at perineal membrane
 - urethra is lined proximally by columnar, distally by squamous epithelium
 - may see mucous-secreting glands of Littre
- Buck's fascia surrounds cavernosal bodies and splits to surround spongiosum ventrally
 - fuses with pubis via suspensory ligament
 - distally it fuses with glans at corona
 - **proximally in perineum it fuses with tunica albuginea and surrounds crura and bulb of spongiosum**
 - penile fracture tears tunica albuginea → contained by Buck's so ecchymosis limited to shaft
 - neurovascular bundles of penis lie DEEP to Buck's fascia
- **penile skin** is highly elastic and without appendages (hair or glandular elements)
 - **blood supply is independent of the erectile bodies and comes from the external pudendal branches of femoral vessels**
 - rich anastomotic network so penile skin is ideal for mobilization on vascular pedicle

What are the layers of tissue surrounding the penis?

- penile skin
- dartos fascia } continuous with Scarpa's fascia & Colle's fascia
- tela subfascialis → very thin CT layer
- Buck's fascia
- tunica albuginea

What are the glands of Tyson?

- preputial glands at coronal sulcus that secrete sebaceous material (smegma when mixed with desquamated epithelial cells)



What is the blood supply to the penis?

- 1) penile skin } external pudendal branch off femoral vessels
 - 2) penis } int. iliac ("OSIOMUII") → int. pudendal (IPP BP/CP") → common penile
 - 1) **dorsal** → cavernous branches to corpora and also circumflex branches to spongiosum and urethra, ending in glans
 - 2) **cavernosal** → straight & helicine arteries to cavernosum
 - 3) **bulbourethral** → spongiosum, urethra, & glans
- } accessory pudendal artery (br. of inferior epigastrics) may also contribute
 } other possible accessory arteries → from ext. iliac, obturator, vesical and femoral

What is the venous drainage of the penis?

- all 3 systems can communicate
- 1) superficial (skin)
 - **superficial dorsal vein** → usually drains to **L saphenous vein**
 - 2) **intermediate**
 - subtunical capillary plexus → emissary → circumflex → **deep dorsal veins (w/in Bucks)**
 - + periurethral veins → **Santorini's plexus** → vesical plexus → internal iliac veins
 - 3) deep
 - **crural, cavernosal, bulbar veins** → internal pudendal veins → internal iliac veins

What is the innervation of the penis?

- **somatics } pudendal nerve (S2-S4)** } inferior rectal, dorsal penile, and perineal (gives off posterior scrotal)
 - dorsal penile nerves provide sensation to penis
 - follow dorsal arteries and richly supply glans
 - run outside pelvis ∴ preserved during pelvic sx
 - perineal nerve branches supply ventral penis
- **autonomics } cavernosal nerves** innervate corporal bodies (NVB)
 - come from pelvic plexus and enter corporal bodies to supply sympathetic (T10-L2) and parasympathetic (S2-S4) innervation
 - sympathetic tone inhibits erections
 - parasympathetics release NO, acetylcholine, VIP that causes smooth muscle and arterial relaxation
 - also controls contraction of bulbocavernosus & ischiocavernosus muscles

Name the different glands that empty into the male urethra.

- 1) prostate gland
- 2) bulbourethral glands (Cowper's) → found posterolateral to membranous urethra in UG diaphragm
→ opens into proximal bulbar urethra
- 3) periurethral glands of Littre → more numerous distally (anterior urethra)
→ form small diverticulae (lacunae of Morgagni)

Scrotum

What does the midline raphe represent?

- runs from meatus to anus and represents fusion of genital tubercles (**urogenital/urethral folds**)

What are the layers of the scrotum?

- skin → pigmented, hair bearing, devoid of fat, rich in sebaceous glands
- dartos → continuous with dartos of penis, Colles' in perineum and Scarpa's in abdomen
- external spermatic fascia → from external oblique fascia
- cremaster muscle and fascia → from internal oblique muscle
- internal spermatic fascia → from transversalis fascia
- tunica vaginalis → from peritoneum

What is a Bell-clapper deformity?

- deficient gubernaculum & testicular mesentery → leaves testis predisposed to torsion

What is the blood supply to the scrotum?

- anterior
 - external pudendal vessels (branch of femoral vessels)
 - don't cross midline raphe
- posterior
 - posterior scrotal branch of perineal vessels (internal pudendal branch)

What is the innervation of the scrotum?

- anterior
 - ilioinguinal (L1) and genitofemoral (L1-L2) nerves
 - don't cross midline raphe
- posterior
 - posterior scrotal branch of perineal nerve (which comes from pudendal nerve)

Why can the testicles & spermatic fascia be preserved during debridement of a Fournier's gangrene?

- different blood supply
- **cremasteric (br of inferior epigastrics), vasal (br of inferior vesical), testicular arteries**

Perineal Lymphatics

What is the lymphatic drainage of the penis, scrotum, and perineum?

- **inguinal nodes**
- superficial & deep
 - separated by the fascia lata
 - superficial connect w/ deep via fossa ovalis, where saphenous joins deep femoral v.
 - most of deep inguinal nodes are medial to femoral
 - deep inguinals drain via femoral ring to external iliac and obturators

What is the difference between the lymphatic drainage of the scrotum and that of the penis?

- scrotal lymphatics DON'T cross median raphe & drain into ipsilateral superficial nodes only
- penile lymphatic drainage can cross over

Testes

Describe the gross anatomy of a testicle

- approx 4x3x2cm with a volume of **25-30mL**
- enclosed by tough capsule made of:
 - 1) **visceral tunica vaginalis**
 - 2) **tunica albuginea**
 - 3) **tunica vasculosa**
- epididymis attaches to posterolateral aspect
- seminiferous tubules → straighten and form rete testis which then form 12-20 efferent ductules
- efferent ductules drain into epididymis → becomes vas deferens
- Leydig cells surround seminiferous tubules in loose tissue → make testosterone in response to LH

What is the spermatic cord composed of?

- vas (found posteriorly)
- testicular artery
- pampiniform plexus and testicular vein
- spermatic fascia and cremasterics
- lymphatics

What is the blood supply to the testis?

- testicular artery → from aorta
- cremasteric artery → from inferior epigastric (external iliac br.)
- vasal artery → from superior vesical (internal iliac br.)
- 3 vessels anastomose near the tail → must be careful with dissection or ligation in this area
- testicular, cremasteric, and vasal veins follow 3 arteries
 - R testicular vein into aorta while L testicular vein drains into L renal vein

What are the distal branches of the testicular artery?

- 1) internal artery
 - 2) inferior testicular artery
 - 3) capital artery → to head of epididymis
- } **best place to Bx testicle is upper or medial aspect of upper pole to avoid vessels**

What is the lymphatic drainage of the testis?

- [illegible]

What is the innervation of the testis?

- visceral innervation travels with gonadal vessels from the renal & aortic plexuses
- additional innervation comes from the pelvic plexus in association with the vas deferens
- genital br. of genitofemoral nerve supplies sensation to tunica vaginalis & overlying scrotum

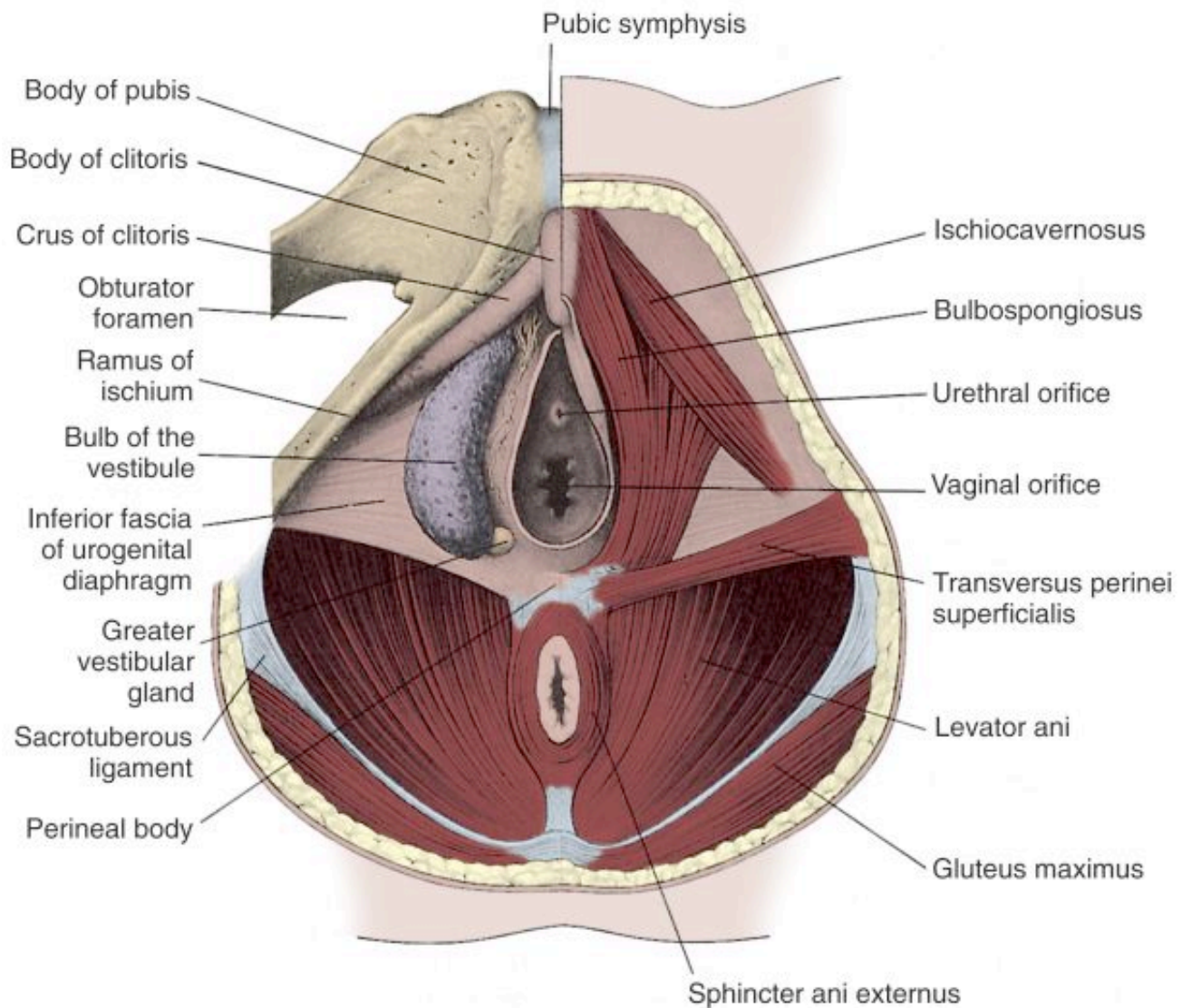
Female Urogenital Triangle

What is the blood supply to the labial fat pads?

- **external pudendal vessels (br of femoral vessels)**
- can be used as rotational flap (Martius) for repair of VVF or urethrovaginal fistula

Describe the contents of the superficial pouch.

- **superficial transverse perinei muscles**
- **clitoris** → **crura** attach to inferior pubic rami
→ surrounded by **ischiocavernosus muscle**
- **vestibular bulbs** → lie on either side of vaginal vestibule and meet at clitoris to form glans of clitoris
→ surrounded by **bulbospongiosus muscle**



Chapter #3 – Hx, P/E, and Urinalysis

HISTORY

What are main aspects of a urologic history?

- chief complaint
- HPI
- PMHx
- FMHx
- meds/allergies

What are the main causes of GU-related pain?

- obstruction eg stones, AUR, tumours, etc
 - not all obstruction is painful, especially when chronic
- inflammation eg pyelonephritis, prostatitis, epididymitis
 - pain is from distension of capsule surrounding organ
- post-op

What is the cause of renal colic & associated N/V?

- acute distension of renal capsule & collecting system } obstruction or inflammation
 - } mediated by PGs
 - pain not changed with movement
 - may radiate to groin
- get **GI symptoms from stimulation of celiac ganglion**

What is the cause of lower GU tract pain?

- bladder } inflammation or AUR
 - constant S/P pain usually not of GU origin, unless related to AUR
 - can get strangury (sharp S/P pain at end of micturition) with cystitis
- prostate } inflammation
 - } poorly localized pain often associated with LUTs
- penis } often referred from distal ureter, bladder, urethra
 - local pain can be from paraphimosis, priapism, Peyronie's disease, etc
- testis } primary or referred
 - torsion, orchitis
 - ureteric stone, hernia
 - } chronic pain usually associated with non-inflammatory conditions (hydrocele, varicocele, etc)

Define significant hematuria?

- gross hematuria or microscopic hematuria with **>3 RBCs per HPF**
 - malignancy until proven otherwise

What are the significant points regarding hematuria?

- 1) gross vs micro
- 2) timing of hematuria
- 3) any associated pain
- 4) clots
- 5) clot shape

What is the significance of the timing of hematuria?

- suggests location of source of bleeding
- total } likely from bladder or upper tracts
- initial } usually urethral
- terminal } likely from prostatic urethra or BN

What are the common LUTS on presentation?

- storage } frequency, urgency, nocturia
- voiding } weak stream, PV dribbling, intermittency, hesitancy, straining, incomplete emptying, dysuria

What is the difference between the AUA symptom score and the I-PSS?

- asks about urinary symptoms over the past month
- AUA symptom score has 7 domains
 - frequency, urgency, nocturia, weak stream, intermittency, straining, sense of incomplete emptying (“**FUNWISE**”)
 - each scored 0-5 for a total out of 35
 - 0-7 = mild LUTS
 - 8-19 = moderate LUTS
 - 20-35 severe LUTS
- **IPSS includes an additional QOL question } scored 0-6**

What are the common patterns of incontinence on presentation?

- total, continuous incontinence
- urge incontinence
- stress incontinence
- mixed incontinence
- overflow incontinence

What are the signs suggestive of PSYCHOGENIC ED?

- acute onset
- associated stressors
- + nocturnal/morning erections
- situational/intermittent ED
- younger men
- no significant RFs (CAD, HTN, DM, etc)

What are the common causes of ANEJACULATION (sympathetics)?

- 1) androgen deficiency
- 2) sympathetic denervation (surgical or related to DM)
- 3) meds (eg α -blockers, psych meds)
- 4) BN and/or prostate surgery

What are the common causes of ANORGASMIA?

- 1) **psychogenic (most common)**
- 2) psych meds
- 3) impaired pudendal nerve function (loss of penile sensation)

What is the significance of hematospermia?

- almost always from nonspecific inflammation of the prostate and/or SVs
 - resolves spontaneously within several weeks
- no further work-up required, unless persists >several weeks
 - r/o genital TB, PCa, TCC of prostate } physical exam, DRE, PSA, urine cytology

What are the common causes of PNEUMATURIA?

- 1) recent instrumentation
- 2) fistula } hx of diverticulitis, IBD, sigmoid Ca
- 3) infections in DM (fermentation of high sugar in urine)

What are some meds with common urological side effects (CHART)?

- 1) decreased libido and ED } anti-HTN'sives eg HCTZ, propranolol
 } psych meds eg SSRIs, benzos
- 2) anejaculation } α -blockers eg prazosin, tamsulosin
 } psych meds eg α -methyldopa, phenothiazines, antidepressants
- 3) priapism } psych meds eg phenothiazines, trazadone
 } anti-HTNsives eg hydralazine, prazosin
- 4) decreased spermatogenesis } chemo eg alkylating agents (cisplatin)
 } drugs affecting endocrine function eg antiandrogens, PGs
 } recreational drugs eg weed, EtOH, nicotine
- 5) incontinence or impaired voiding } smooth muscle relaxants/stimulants
 } striated muscle relaxants eg baclofen, diazepam
- 6) urinary retention } anticholinergics eg oxybutynin
 } CCBs eg nifedipine
 } anti-Parkinson's meds eg carbidopa, levodopa
 } α -agonists eg pseudoephedrine, phenylephrine
 } antihistamines eg loratadine, diphenhydramine
- 7) ARF } antibiotics eg aminoglycosides, penicillins, cephalosporins, amphotericin
 } chemo eg cisplatin
 } others eg NSAIDs, ACEi, phenytoin
- 8) gynecomastia } antiHTN'sives eg verapamil
 } cardiac meds eg digoxin
 } GI drugs eg cimetidine, metoclopramide
 } psych meds eg phenothiazines, amitriptyline, imipramine

What are the common urologic sequelae of chronic, heavy EtOH consumption?

- urinary & sexual dysfunction } autonomic & peripheral neuropathy
- testicular atrophy, decreased libido, ED } ↓'d T from impaired hepatic metabolism of estrogen
- hematuria/bleeding issues } coagulopathy from hepatic toxicity
- post-op Dts } withdrawal

PHYSICAL EXAM

What is the DDx of a systolic bruit over the upper abdomen?

- RAS
- renal artery aneurysm
- large renal AVF

What are the signs suggestive of a suspicious varicocele?

- | | | |
|---|-------|---|
| 1) sudden onset of varicocele | \ } / | suspicious for retroperitoneal mass
compressing drainage of spermatic vein |
| 2) R-sided varicocele | | |
| 3) varicocele that doesn't reduce with recumbency | | |

What are the important steps of a DRE?

- external examination of anal area
- assessment of anal sphincter tone
- prostate exam
- circumferential rectal exam to r/o rectal malignancies
- +/- FOBT

What are the important steps of a female pelvic exam?

→ should always have a female RN present

- external examination } atrophic changes, erosions, ulcers, discharge, warts
 } urethral caruncles, mucosal hyperplasia, mucosal prolapse
- Valsalva maneuvers } cystocele or rectocele
- cough test } SUI
- palpation of urethra } masses, diverticula
- bimanual exam } bladder, uterus, adnexa

What is the bulbocavernosus reflex (BCR)?

- tests integrity of spinal cord-mediated reflex arc involving **S2-S4**
- finger in rectum
- squeeze glans penis or clitoris or pull on catheter
- +ve if tightening of anal sphincter } reflex intact

URINALYSIS

What is an acceptable method of urine collection for analysis?

- adult male } MSU (with retracted foreskin)
- adult female } MSU (with separated labia)
 } if infection suspected, need CIC sample
- kids } depending on age, CIC or S/P aspiration

What is the Stamey 4-part urine sample?

- VB1 } initial 5-10cc of voided urine → urethral bugs
- VB2 } MSU → bladder bugs
- EPS } expressed prostatic secretions (post-prostate massage) → prostate bugs
- VB3 } initial 2-3cc of voided urine after prostatic massage → prostate bugs

What are some of the common causes of abN urine colour (CHART)?

- 1) clear } overhydration
 } very dilute urine
- 2) **cloudy/milky** } **phosphaturia (most common) → clears in acidic urine**
 } pyuria
 } chyluria
- 3) red } hematuria
 } hemoglobinuria/myoglobinuria
 } beets & blackberries (anthrocyanin)
 } chronic lead & mercury poisoning
 } rifampin
 } phenothiazines
- 4) orange } dehydration
 } phenoazopyridine (Pyridium)
 } sulfasalazine
- 5) yellow } normal (urochrome)
 } riboflavin (vitamins)
- 6) green-blue } biliverdin
 } indigo carmine
 } methylene blue
 } amitriptyline
 } triamterene
 } phenosis (eg iv cimetidine)
- 7) brown or black } urobilingen
 } porphyria
 } chloroquine and primaquine
 } flagyl
 } nitrofurantoin
 } alcaptonuria
 } hemorrhage
 } methyldopa

What is the normal urine OSMOLALITY?

- reflection of hydration status but better indicator of renal function than specific gravity
- value is affected by same factors as specific gravity
- **range is 50 to 1200 mOsm/L**

What is the normal urine SPECIFIC GRAVITY?

→ reflection of hydration status and some info on renal []'ing ability

- **normal range = 1.001 to 1.035**

→ fixed specific gravity of 1.01 is a sign of renal insufficiency

- can be increased due to:

→ dehydration

→ DM (glucosuria)

→ SIADH

→ post iv contrast

→ post iv dextran

- can be decreased due to:

→ increased fluid intake

→ diuretics

→ decreased renal concentrating ability

→ DI

What is the normal urine pH?

→ **usually reflects serum pH } except in RTA**

- alkaline urine despite serum being acidemic

- Dx made with inability to acidify urine below pH of 5.5 after acid load

- **normal range = 5.5 to 6.5**

- may also help in UTIs and stone disease

→ presumed UTI + urine pH >7.5 likely suggests infection with urea-splitting organism such as *Proteus*

→ stones + urine pH <5.5 may suggest uric acid stones

→ can be used to assess alkalinization Rx for uric acid & cystine stones

What is the definition of HEMATURIA?

- **anything >3 RBCs per HPF**

How can hematuria be distinguished from hemoglobinuria & myoglobinuria?

- microscopy of centrifuged urine } presence of large # of erythrocytes = hematuria

- serum exam } pink supernatant after centrifugation = hemoglobinuria

} clear supernatant after centrifugation = myoglobinuria

What are some causes of a FALSE +VE DIPSTICK reading for hematuria?

- contamination of urine with menstrual blood

- vigorous exercise

- dehydration

- hemoglobinuria/myoglobinuria

What are the signs suggestive of hematuria of a nephrologic origin?

→ nephrologic hematuria has more significant proteinuria (minimal seen in urologic hematuria)

1) glomerular } dysmorphic erythrocytes (seen on light phase microscopy), RBC casts, proteinuria

2) non-glomerular (tubulointerstitial, renovascular, systemic) } uniformly round erythrocytes, no RBC casts, proteinuria

Which glomerular diseases are associated with glomerular hematuria (CHART)?

1) **IgA nephropathy (Berger's disease) – 30% (most common)**

2) mesangioproliferative GN – 14%

3) focal segmental proliferative GN – 13%

4) familial nephritis (Alport's syndrome) – 11%

5) membranous GN – 7%

6) mesangiocapillary GN – 6%

7) FSGS – 4%

8) unclassifiable – 4%

9) SLE – 3%

10) post-infectious GN – 2%

What is the most common cause of glomerular hematuria?

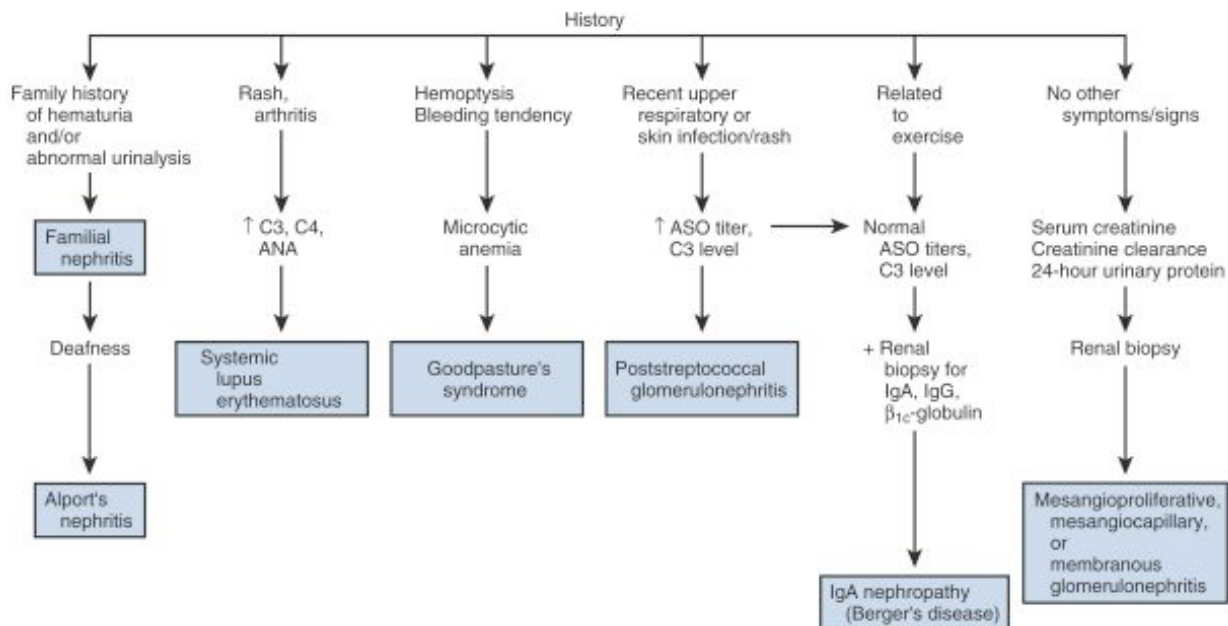
➔ **IgA nephropathy (~30%)**

- most commonly in M kids, young adults
- intermittent gross hematuria but constant microhematuria } usually have no associated systemic symptoms
- } may have low-grade fever or rash
- } may present after exercise
- good prognosis } **only 25% will develop renal insufficiency**
- } older age at onset, initial abN creatinine, consistent proteinuria, HTN are all poor prognostic indicators
- similar presentation to Henoch-Schonlein purpura, SLE, bacterial endocarditis, Goodpasture's

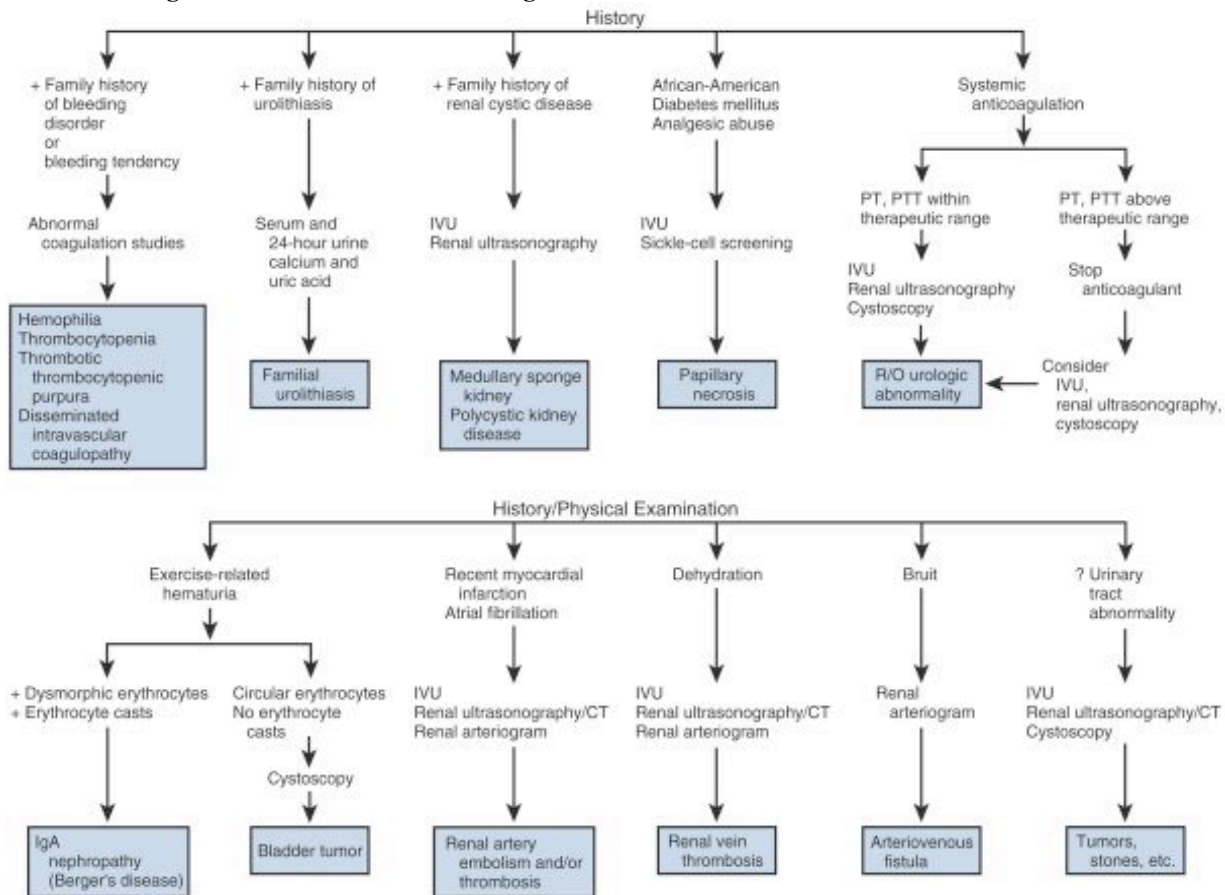
What are the non-glomerular diseases associated with hematuria?

- tubulointerstitial
 - MSK
 - nephrocalcinosis
 - AD PCKD
- renovascular
 - renal artery embolism and/or thrombosis
 - renal vein thrombosis
 - AVF
- systemic
 - hemophilia
 - thrombocytopenia
 - TTP
 - DIC
- urologic/surgical
 - tumours
 - UTIs
 - stones
 - trauma
 - papillary necrosis (DM, blacks with sickle cell, analgesic abusers, etc)

What is the algorithm for evaluating glomerular hematuria?



What is the algorithm for evaluation of non-glomerular hematuria?



What are the AUA guidelines on microscopic hematuria?

➔ **microscopic hematuria = ≥ 3 RBC/hpf from a fresh MSU**

1) high-risk patients

➔ microscopic hematuria x1 warrants FULL UROLOGIC EVALUATION

- hx and P/E
- urine cytology
- upper tract imaging
- cystoscopy

➔ high risk includes:

- smoking hx
- hx of gross hematuria
- hx of urologic dz
- hx of UTI
- hx of pelvic RADs
- occupational exposure
- age >40yrs
- hx of irritative symptoms
- analgesic abuse

2) low-risk

➔ if suggestion of benign cause (UTI, intercourse, menstruation, vigorous exercise) then REPEAT U/A 48hrs AFTER CESSATION OF ACTIVITY

➔ otherwise:

- UPPER TRACT IMAGING
- URINE CYTOLOGY

3) presence of significant proteinuria (>1g/day), RBC casts, or renal insufficiency warrants REFERRAL TO NEPHROLOGIST

4) if -ve evaluation, repeat U/A, URINE CYTOLOGY, and BP check at 6, 12, 24, 36 months

→ microscopic hematuria = ≥ 3 RBC/hpf on 2 u/a

- ### What are the normal components of urinary PROTEIN?

- 30% albumin
- 30% serum globulins
- 40% tissue proteins } Tamm-Horsfall protein is major component

- 1) glomerular (**most common type**)

- What tests can be done to differentiate glomerular, tubular, and overflow proteinuria?

- What are the potential causes for a FALSE –VE reading for PROTEINURIA on dipstick?

- What are the potential causes for a FALSE +VE reading for PROTEINURIA on dipstick?

- alkaline urine
- highly concentrated sample
- significant gross hematuria
- antiseptic cleanser in urine
- contrast agents in urine

What is the work-up for proteinuria?

1) transient proteinuria

- occurs commonly, especially in kids } usually resolves spontaneously within days
- from fever, exercise, emotional stress, or CHF

W/U } repeat urinalysis

→ normal = no further work-up

→ persistent = evaluate as persistent proteinuria

2) intermittent proteinuria

- often related to postural change } common in young males
- } possibly due to ↑'d pressure on renal vein during standing
- } resolution of proteinuria with recumbency

- degree of proteinuria usually not too high (<1g per day)

W/U } repeat urinalysis standing and lying

→ orthostatic proteinuria + N renal function = no further work-up

→ not orthostatic = evaluate as persistent proteinuria

3) persistent proteinuria

W/U } 24hr-urine protein

→ $>2\text{g/day}$ + mostly albumin = GLOMERULAR (most common cause of proteinuria)

→ 300mg to 2g/day + mostly LMW proteins = TUBULAR vs OVERFLOW

- } urine immunoelectrophoresis

→ normal proteins = TUBULAR

→ abN proteins = OVERFLOW

- } evaluate specific protein abN'ity

→ Bence-Jones (light chain immunoglobulins) = multiple myeloma

→ hemoglobin = hemoglobinuria

→ myoglobin = myoglobinuria

What is the level of serum glucose required to have GLUCOSURIA?

- glucose detectable in urine at serum level **>180 mg/dL (~10 mmol/L)**

What enzymes are involved in detecting glucosuria on dipstick?

→ specific for glucose with no cross-reactivity

- 1) **glucose oxidase** } glucose \rightarrow gluconic acid + hydrogen peroxide
- 2) **peroxidase** } hydrogen peroxide \rightarrow colour change on stick

What KETONES are excreted in the urine?

→ **not normally found in urine** } appears in urine (before serum) with abN fat breakdown

- 1) **acetoacetic acid** } only one to be detected on dipstick
- 2) acetone
- 3) β -hydroxybutyric acid

What are the causes of ketonuria?

- DKA
- pregnancy
- after period of starvation
- rapid weight reduction

What are the potential causes of FALSE +VE URINE KETONES on dipstick?

- very acidic urine
- very []'d urine
- abN coloured urine
- taking levodopa
- taking 2-mercaptoethane sulfonate sodium

What kind of BILIRUBIN is present in urine?

→ **normally, no bilirubin found in urine** } very small amounts of urobilinogen

1) direct/conjugated bilirubin } made in hepatocyte

} LMW and water soluble

→ can be present in urine if there is **intrinsic hepatic disease or**

obstruction of bile ducts

2) urobilinogen } end product of conjugated bilirubin metabolism

} conjugated bilirubin is metabolized in bowel to urobilinogen

} 50% excreted in stool & other 50% reabsorbed into enterohepatic circulation

} 1-4 mg /day escapes hepatic uptake and is excreted in urine

→ can be present in urine in high amounts if **hemolysis or liver disease**

→ low levels in urine if bile duct obstruction or Abx that alter bowel flora

What are the potential causes of a false reading of bilirubin on dipstick?

→ FALSE -VE

- presence of ascorbic acid

→ FALSE +VE

- phenazopyridine (Pyridium)

What is the importance of LEUKOCYTE ESTERASE and NITRITE tests on dipstick?

→ used to screen for UTI

- leukocyte esterase } produced by **neutrophils**

} test for pyuria

- nitrites } nitrates converted to nitrites by mainly **GN bacteria**

} strongly suggestive of bacteriuria (>90% specificity, but low sensitivity)

List causes of a FALSE +VE nitrite test.

- contamination (skin, vaginal, etc)

- Pyridium

- old urine

- dipstick exposed to air

List causes of a FALSE -VE nitrite test.

- increased urinary specific gravity

- increased urobilinogen

- bacteria lacking nitrate reductase enzyme (Strept is #1, then Enterococcus, then Staph)

- acidic urine pH (<6.0)

- Vit C supplementation

- Low nitrate diet

What is the definition of PYURIA?

- men } **>2 leukocytes per HPF**

- women } **>5 leukocytes per HPF**

List the potential causes of sterile pyuria

→ INFECTIOUS

- GU TB

- UTI with fastidious organism

- UTI but on ABx

- class 3 chronic prostatitis

- parasitic infections

- Chlamydia urethritis

- adjacent appendicitis

→ NON-INFECTIOUS

- stones

- renal papillary necrosis

- GU sarcoidosis

- tumour

- PCKD

- AIN

- post-RADs cystitis

- post-cyclophosphamide cystitis

- interstitial cystitis

What are the potential causes of a false reading for WBCs on dipstick?

- FALSE -VE
 - increased urine specific gravity
 - glycosuria
 - presence of urobilinogen
 - meds that change urine colour
 - high intake of ascorbic acid
- FALSE +VE
 - contamination of specimen

What are the important things to look for on microscopy?

- perform under low-power (100x) and high-power (400x)
- look at edges, where casts and other elements tend to concentrate

1) low-power

- RBCs
- WBCs
- casts
- cystine crystals (hexagonal)
- oval fat macrophages
- parasites (eg *Schistosoma hematobium* and *Trichomonas vaginalis*)

2) high-power

- to differentiate round (non-glomerular) vs dysmorphic (glomerular) RBCs
- all other crystals
- bacteria
- yeast

What type of CASTS are seen on microscopy?

→ **Tamm-Horsfall mucoprotein is basic matrix for all renal casts } always present in urine**

- 1) hyaline casts } only mucoproteins
 } normal
- 2) RBC casts } entrapped erythrocytes + mucoproteins
 } glomerular bleeding
- 3) WBC casts } entrapped leukocytes + mucoproteins
 } acute glomerulonephritis, acute pyelonephritis, AIN
- 4) heme-granular casts } ATN
- 5) fatty casts } nephrotic syndrome, lipiduria, hypoT4
- 6) cellular casts } nonspecific renal damage

What type of urinary CRYSTALS are seen on microscopy?

- acidic urine
 - COM } hourglass/dumbbells → you'd be a dumbbell to SWL COM stones
 - Ca oxalate dihydrate } tetrahedral, envelope → pay COD when you get your envelope
 - cystine } hexagonal (benzene) → you are Hex'd since birth with cystine stones
 - only seen at low-power
 - uric acid } amorphous shards, plates → shards of uric acid
- alkaline urine
 - struvite } rectangular, coffin-lid → dead in a coffin if you get struvite stones
 - Ca phosphate-apatite } amorphous
 - Ca PO₄ dihydrate (brushite) } needle-shaped → brushes have needle-shaped bristles

How many BACTERIA are needed to make the Dx of a UTI?

- women } **5 bacteria per HPF** (reflects ~100,000 colonies/mL)
- men } **any bacteria**

What types of cells in the EPS specimen are suggestive of prostatic infection?

- leukocytes
- oval fat macrophages

Chapter #4 – GU Imaging

CONVENTIONAL RADIOGRAPHY

What is plain x-ray used for in urology?

- KUB xray
- cystography (eg VCUG)
- RUG
- IVP
- retrograde & antegrade pyelogram
- loopography

What are the main uses of plain film xray?

- stones } not ideal diagnostic test
 - false-negative if stone lies over bone, if radiolucent stone, or small stone
 - false-positives from vascular calcifications and phleboliths
- } good to follow known stones and to determine lucency of stone prior to SWL
- FB's within GU tract
- assessment of stents, catheters, drains

What is the approach to reading a KUB xray?

- 1) organ outlines } liver, spleen, kidneys, bladder
 - } displacement of normal structures
- 2) stomach & bowel gas
- 3) soft tissue abN'ities } flank stripe = thin layer of retroperitoneal fat b/w lateral abdo wall and intraperitoneal contents
 - displaced or enlarged by retroperitoneal fluid collection
 - } psoas shadow = absent with retroperitoneal mass/fluid
 - } soft tissue masses
- 4) spinal & bony pelvis } spina bifida, sacral agenesis, fractures, mets

What are the different types of iodinated contrast media used in urology?

- all derive from a **2,4,6-triiodinated benzene ring with a carboxyl group at the 1-position**
- **radio-opaque because dense molecules able to absorb X-rays**
- **initially causes renal arteriolar vasodilation (short-lived) then vasoconstriction**
- 1) differing side chains at the 3- and 5-positions represent different brands
- 2) ionic vs non-ionic
- 3) high-osmolar vs low osmolar
 - **low osmolar, non-ionic forms better** } lower osmotic load + lower complications
 - } hydrophilic hydroxyl group instead of carboxyl
 - } eg Omnipaque, Isovue, Optiray
 - more complications with high-osmolar, ionic contrast } eg Hypaque, Conray
 - iso-osmolar, non-ionic } eg Visipaque

What are the main advantages of low-osmolar contrast media?

- less nephrotoxic } **excreted by glomerular FILTRATION**
- less N/V
- better for patients with a hx of allergy to contrast, hx of asthma, heart disease (CHF)
- can be used for myelography (ionic contrast cannot)
- more hydrophilic so less likely to cross cell membranes, BBB, etc
- ? less urticaria, flushing, pain at injection site
- way more expensive

What are the physiologic effects of high-osmolar contrast?

- 1) CVS } increased CO
 } decreased PVR + reflex tachycardia
 } bradycardia (vagal)
- 2) hematologic } inhibition of coagulation cascade
- 3) renal } osmotic diuresis
 } biphasic response → vascular dilation followed by vasoconstriction
 → leads to transient decrease in GFR

List adverse reactions to contrast media.

- | | |
|-------------------------------------|-------------------------------------|
| → minor idiosyncratic reactions | → major idiosyncratic reactions |
| - itching | - bronchospasm |
| - N/V | - arrhythmias |
| - diaphoresis | - death |
| - urticaria | - seizures |
| - cough | - syncope/shock |
| - edema (facial) | - edema (pulmonary, laryngeal) |
| → minor non-idiosyncratic reactions | → major non-idiosyncratic reactions |
| - vasovagal | - bradycardia |
| - metallic taste | - nephropathy |
| - N/V | - cardiotoxicity |
| - extravasation | - shock |
| - warm sensation | |
| - delayed flu-like symptoms | |

What are the major adverse reactions associated with contrast media?

- can be idiosyncratic or dose dependent
- **occurs in up to ~10%** } most are mild & less common with low osmolar, nonionic contrast media
- 1) allergic reactions } **anaphylactoid (not Ig mediated so not anaphylactic)**
 - urticaria (hives), facial edema
 Rx → antihistamine
 - bronchospasm, pulmonary edema
 Rx → β-agonists or epinephrine
 - 2) cardiovascular toxicity } EKG changes, depressed myocardial contractility, depression of SA & AV nodes, arrhythmia, ischemia
 → less common by avoiding bolus injections & using low osmolar, nonionic contrast media
 - 3) renal toxicity } <1% if normal renal function
 } pathogenesis unknown
 → likely multifactorial
 → less common w/ low osmolar, nonionic contrast media
 → less common w/ renoprotective measures } fluid bolus, mucomyst, NaHCO₃

What are the RFs for development of, or increased severity of, contrast nephropathy?

- defined as impaired renal function within 48hrs of contrast administration
- listed approximately in order (from proven to theoretical) } } } "RADD Nephrotoxic CHAMP"
- **Renal insufficiency (most predictive)**
 - Age >65
 - DM } must hold metformin x 48hrs (risk of lactic acidosis if renal failure occurs)
 - Dehydration
 - concurrent **nephrotoxic** drugs (eg ACE inhibitors, cyclosporine, NSAIDs, etc)
 - CHF
 - HTN
 - Amount of contrast used (high) or recent contrast use
 - Multiple myeloma/ hyperuricemia
 - Proteinuria

What are the RFs associated with an idiosyncratic reaction to contrast?

- “SHAAP”
- 1) **S**hellfish allergy
- 2) **H**igh-osmolar contrast used
- 3) **A**sthma
- 4) **A**topy
 - hay fever, food allergies, etc
- 5) **P**revious reaction
 - risk of subsequent reaction is 3-4x greater

What methods can decrease the likelihood of an adverse reaction to iv contrast?

- 1) avoid contrast if possible } CO₂ angiography
- 2) use LOW OSMOLAR, NON-IONIC contrast } use minimum amount possible
- 3) avoid multiple exposures within short duration of time
- 4) pretreatment strategies } hydration → NS, NaHCO₃ (3amps in 1L D5W 6cc/kg 1hr prior,
then 1cc/kg x 6hrs post)
 - } mucomyst (600mg po bid x 2days)
 - } steroids +/- benadryl
- 5) stop nephrotoxic meds } NSAIDs, ACEi, etc
- 6) post-treatment strategies } hemodialysis
 - if done early, may decrease risk of nephropathy

What are the indications for IVP?

- 1) hematuria
- 2) stones
- 3) trauma } one-shot IVP at 10 mins after 2ml/kg

What are the controversies regarding preparation for IVP?

- bowel prep } no benefit on randomized studies
 - } may be consideration for those with chronic constipation
- dehydration } improves imaging but can be risky, especially in those with renal insufficiency
 - } overhydration not good for visualization either
 - } NPO after MN should be sufficient

What are the different images taken as part of an IVP?

- 1) **scout film** (supine) } renal outline, stones, etc
- 2) nephrogram } taken within **2-3 minutes** of injecting **50-100mL of iv contrast medium**
 - } tomogram looks at renal parenchyma
- 3) pyelogram } begins at ~**5mins** (contrast should be within collecting system)
 - } can use compression device to distend collecting system
 - } 5min film then subsequent films based on individual pt (eg 10min, 15min, etc)
 - } **30 min drainage film** after release of any compression devices
- 4) oblique films } to visualize collecting system in relation to filling defects, calcifications, etc
- 5) prone films } better images of ureter
- 6) upright films } to identify renal ptosis or layering of contrast in severely hydronephrotic systems
- 7) post-void film } to assess bladder and bladder outlet

What is a limited IVP?

- mainly for pregnancy } shield contralateral to side of interest
- 1) scout film
- 2) film at 20-30 seconds
- 3) film at 20-30 minutes

What is the DDx of non-visualization of one kidney during IVP?

- absence of kidney } congenital agenesis
- } ectopic kidney
- } Nx
- decreased perfusion } unilateral renal vein thrombosis
- } renal artery occlusion/thrombosis
- } pedicle avulsion (trauma)
- } systemic hypoTN (uncommonly unilateral)
- high-grade obstruction } chronic obstructive uropathy
- replaced normal renal parenchyma } MCDK
- } renal tumour
- } XGP
- } chronic pyelonephritis

What are the cause of nephrocalcinosis?

- CORTICAL (uncommon)
 - Cortical necrosis (acute)
 - primary Oxalosis
 - chronic Rejection
 - Toxins (ethylene glycol, etc)
 - Insufficiency of pyridoxine (B6)
 - Chronic GN
 - Alport's syndrome
 - sickLe cell disease
- MEDULLARY
 - **distal RTA (2nd most common)**
 - **MSK (common)**
 - sarcoidosis
 - excess vitamin D
 - renal TB
 - renal papillary necrosis
 - Dent's disease
 - Paget's disease
 - other causes of hypercalcemia
 - **1° hyperPTH (most common)**
 - immobilization
 - malignancy
 - hyperT4
 - pheochromocytoma
 - milk-alkali syndrome
 - Vitamin A, Vitamin D
 - meds (steroids, HCTZ, Li, E)

What are the indications for loopography?

- to assess conduit itself or to assess upper tracts (refluxing anastomosis only)
- hematuria
- stones
- stomal stenosis
- urinary fistulae/leaks
- uretero-enteric anastomotic strictures
- hydronephrosis
- surveillance for TCC
- loop ischemia

What are the indications for static cystography?

- mainly in post-op patient and trauma patient } being replaced by CT cystograms
- bladder lesions
- bladder rupture
- urine leak
- urinary fistulae

What are the different films taken as part of a static cystogram?

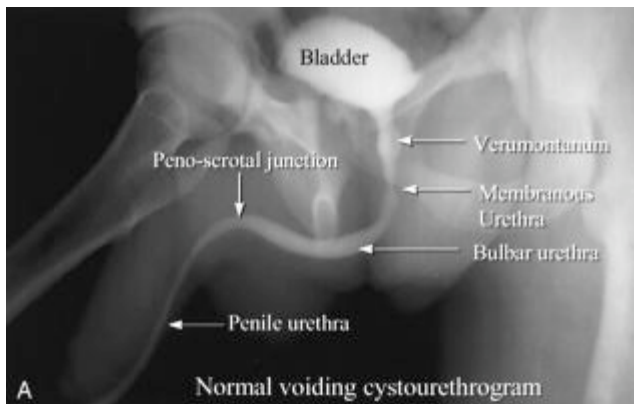
- 1) scout film
- 2) fill views } AP + lateral/oblique
- } minimum 350cc contrast (or until pain)
- 3) drainage film

What are the indications for VCUG?

- | | | | |
|-----------|-------------------------|-------------|---------------------|
| 1) peds } | UTIs | 2) adults } | urethral strictures |
| | } VUR | | } bladder ties |
| | } ureterocele | | } urethral tics |
| | } PUVs | | |
| | } dysfunctional voiding | | |

What are the different films taken as part of a VCUG?

- 1) scout film
- 2) bladder fill views } early fill & late fill (AP)
- 3) voiding film } AP + oblique
- 4) post-void film



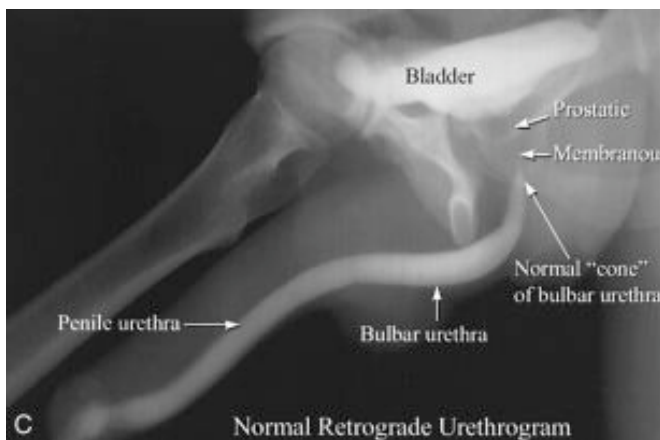
→ NORMAL VCUG

What are the indications for RUG?

- 1) urethral trauma
- 2) urethral strictures
- 3) urethral diverticula
- 4) urethral fistulae

How do you perform a RUG?

- patient in oblique position (30-45 degrees)
- dependent hip acutely flexed & rotated externally; other leg straight
- 8-10Fr foley inserted in fossa navicularis and inflated with 1-2cc
- 30-50% contrast gently injected at 10cc increments



→ NORMAL RUG

What are the indications for a retrograde pyelogram?

- 1) hematuria
 - 2) upper tract TCC surveillance
 - 3) ureteric injury/strictures
 - 4) ureteric fistulae
 - 5) ureteric stent placement
 - 6) stones
- allergy to iv contrast

What are the patterns of renal backflow seen with retrograde pyelography?

- 1) pyelotubular (intrarenal backflow)
→ contrast into CCT
- 2) pyelosinus
→ extravasation into renal sinus from overdistension
- 3) pyelolymphatic
→ opacification of fine lymphatic channels in renal hilum
- 4) pyelovenous
→ contrast enters venous channels
- 5) forniceal rupture

ULTRASOUND

What are the main advantages of U/S?

- cheap & easy
- non-invasive
- no radiation
- no contrast
- good resolution

What is the benefit of high frequency transducers (eg >7 Hz)?

- higher resolution } BUT depth of penetration decreases

List lesions that appear hyperechoic (WHITE) on U/S.

- fat
- stones
- gas
- bones

What is the typical appearance of renal structures on U/S?

- renal parenchyma } medullary pyramids are less echogenic (darker) than cortex
 - } corticomedullary differentiation more apparent in kids
 - } cortex becomes hyperechoic with scarring
- renal sinus fat } hyperechoic
- renal capsule } hyperechoic
- collecting system } hypoechoic
- simple cysts } anechoic + no echogenic foci

What are the U/S criteria for a simple renal cyst?

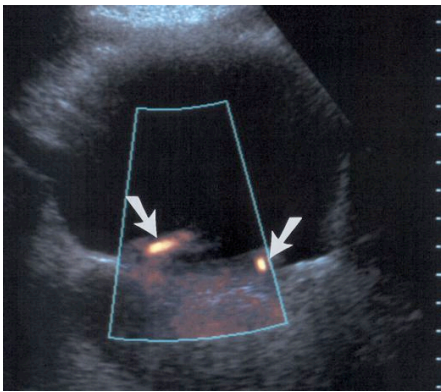
- anechoic
- well defined posterior wall
- enhanced through transmission
- no internal vascular flow on Doppler
- no septations
- no solid components

Why is U/S useful to assess the adrenal gland in kids?

- 1) lack of retroperitoneal fat
- 2) relatively larger in kids
- R adrenal usually easier to see than L due to acoustic window provided by liver
- **adrenal cortex is hypoechoic (dark)**
- **adrenal medulla is echogenic**
- CT or MRI preferred in adults

What are the benefits of bladder U/S?

- visualization enhanced with full bladder
- assessment of PVR
- gross assessment of bladder wall (normal = 4-6mm)
- identification of intravesical lesions (eg stones, ureterocele, etc)
- identification of ureteric jets (Doppler U/S) } should be seen within 15 mins of observation
 } technically difficult and may be present even w/ partial
 ureteric obstruction



→ DOPPLER U/S OF BLADDER } URETERIC JETS

What are some indications for scrotal U/S?

- acute scrotum } eg torsion vs epididymo-orchitis
- testicular mass
- paratesticular mass
- varicocele
- hernia
- hydrocele

What is the typical appearance of scrotal structures on U/S?

- testis } granular homogeneous appearance measuring ~4cm x 3cm
 - } good Doppler flow
 - increased in orchitis
 - absent in torsion
- hydrocele } hypoechoic fluid
- epididymis } isoechoic or hyperechoic
 - less flow cf testis, unless epididymitis
- appendix testis } only seen if abN
- varicocele } only visible if >2mm

What is the role of urethral U/S?

- urethral strictures
 - urethral diverticulum
- correlates fairly well with MRI

What are the main advantages of CT over IVP?

- ### What are the 3 phases of a triphasic CT to assess renal masses?

→ fat is $< -20\text{HU}$ on CT

- } arteriosclerosis

[illegible]

What is the minimum CrCl necessary for contrast CT to be performed safely?

- non-diabetics } CrCl ≥ 30
- diabetics } CrCl ≥ 50

What are the indications for a CT angiogram?

- pre-op for donor Nx
- to assess for crossing vessel causing UPJO
- renal artery stenosis

How do you differentiate an AML from a liposarcoma on CT?

- 1) defect in renal parenchyma } no renal defect with liposarcoma
 - 2) enlarged vessels seen through lesion } no vessels in liposarcoma
- AML has macroscopic fat } lesion should be < -20HU
 → **in AMLs, look for parenchymal notch and feeding vessel**

What does renal lymphoma look like on CT?

- can be similar to RCC } more likely multifocal
- look for other nodal disease → isolated renal involvement is rare
- “classic” CT image is kidney encased in inflammation
- decreased vascularity compared to similar sized RCC

MRI

What are the advantages of MRI over CT?

- 1) no radiation
- 2) no contrast media
- 3) superior soft-tissue resolution
→ not good for stones though

What is the difference between T1 & T2-weighted images?

- T1 images are based on z-axis } measures how fast tissue becomes magnetized
- T2 images are based on xy-axis } measures how fast tissue loses magnetization
- T1 } fluid = dark - T2 } fluid = bright
 } fat = bright } fat = usually dark

Tissue	T1	T2
Fat	High	Less high
Muscle	Low	Low
Adrenal	Medium	Medium
Adrenal Cyst	Low	High
Adrenal Pheo	Medium	Very high
Renal Cyst	Low	High
Renal Hemorrhagic Cyst	High	High
Tumor	Medium	Higher (variable)
Blood fast flow	Low	Low
Blood slow flow	Medium to high	High
Tumor thrombus	Medium	Medium

What are the contraindications to MRI?

- pacemakers
- intracranial aneurysmal clips
- cochlear implants
- retained metal FBs
- metallic prostheses
- morbid obesity } can't fit in gantry
- claustrophobia } relative → may need sedation

What is the issue with Gadolinium and renal insufficiency?

→ case reports of **nephrogenic systemic fibrosis (NSF)**

- almost exclusively in renal insufficiency or renal failure
 - } being on dialysis doesn't matter
 - } only a few cases unrelated to renal failure

- subacute swelling of distal extremities initially
- severe skin induration develops over next few weeks
- can get constant pain, muscle restlessness & loss of skin flexibility
- can also involve other organs } liver, lungs, muscles, heart

What is the main indication for BLADDER MRI?

- assessment of invasion of bladder wall } TCC
- } other pelvic neoplasms
- **need T2-weighted imaging** } urine is bright

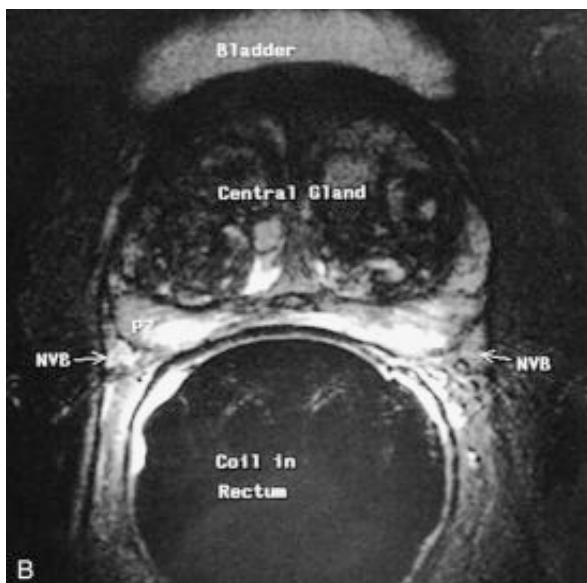
What is the role of PROSTATE MRI?

→ mainly in study setting } not 1st line

- used with endorectal coils
- **T2-weighted imaging needed } poor intraprostatic detail on T1**
 - PZ is bright
 - DVC is bright
 - CZ is intermediate
 - SVs are bright
- to assess for intraprostatic lesions or capsular penetration

What is the role of URETHRAL MRI?

- strictures in males
- diverticula in females



→ PROSTATE MRI

NUCLEAR SCINTIGRAPHY

Why has technetium-99m (99mTc) tracers replaced 131I-orthoiodohippurate tracers?

- 1) shorter T_{1/2} (6hrs vs 8days)
- 2) better images

What are the common 99mTc tracers used in renal scintigraphy?

- 1) **DTPA } “glomerular tracer”**
 - **100% filtration**
 - good to quantify **GFR** and assess for **obstruction**
 - } only 20% extraction coefficient in mature kidney
 - **not as good when kidney function is low or immature**
- 2) **MAG3 } “tubular tracer”**
 - **~100% tubular secretion (in PCT) } some say 20% filtration**
 - better image quality, more accurate numerical values
 - good to quantify **GFR** and assess for **obstruction**
 - } little cortical retention
 - good for drainage
 - 90% in bladder within 3hrs
 - } **also assesses Renal Plasma Flow (RPF)**
 - } higher extraction fraction (50% in mature kidney)
 - **more accurate when kidney function is poor or immature**
- 3) **DMSA } “cortical tracer”**
 - binds to PCT
 - **65% secretion + 35% filtration**
 - good for assessing **parenchyma (scars, pyelonephritis)**
 - } gives minimal information on GFR
 - **differential function**
 - } **not good for UPJO as doesn't give info on drainage } + cortical retention**

What are the advantages of MAG3 over DTPA for diuretic renal scanning?

- more useful in immature kidneys
- more accurate in renal insufficiency patients
- DTPA is way cheaper

What other renal scans are available?

- 1) glomerular tracers
 - 99mTc-GHA (glucoheptonate) } glomerular + cortical tracer
 - ⁵¹Cr EDTA
 - ¹²⁵I Iothalamate
- 2) tubular tracers
 - 131I-OIH (iodohippurate) } **BEST to estimate RPF**
- 3) cortical tracers
 - 99mTc-GHA (glucoheptonate) } glomerular + cortical tracer

What are the indications for renal scintigraphy?

- pre-op renal differential function (eg chronic pyelonephritis, UPJO, ureteric stricture, etc)
- ARF
- urine leak
- RVH
- chronic pelvicaliectasis (differentiating obstruction)
- pyelonephritis

Chapter #6 – Instrumentation and Cystoscopy

URETHRAL CATHETERIZATION

List some indications for urethral catheterization

- 1) diagnostic
 - collection for C&S in women
 - measurement of PVR
 - instillation of contrast for imaging studies (eg VCUG, UDS)
 - close monitoring of U/O
 - for UDS
- 2) therapeutic
 - AUR
 - CBI for hematuria
 - decompressing bladder prior to surgery
 - intravesical therapy (eg BCG, MMC, etc)
 - CIC for neurogenic bladder
 - as stent after RP, urethroplasty, etc

What are the different types of catheters?

- 1Fr = 0.33mm in diameter ... 30Fr = 1cm } refers to OUTSIDE CIRCUMFERENCE
- Robinson (CIC)
- Foley
- Whistle-tip
- Coude
- Malecot
- 3-way

URETHRAL DILATATION

List indications for urethral dilatation

- male
 - prior to transurethral surgery
 - urethral stricture
 - BN contracture
- female
 - prior to transurethral surgery
 - voiding dysfunction and recurrent UTIs are NOT INDICATIONS

CYSTOURETHROSCOPY

List some indications for cystourethroscopy.

- evaluation of hematuria
- evaluation of LUTS
- +ve urine cytology
- surveillance for TCC
- assessment of urethral strictures prior to Sx
- retrograde imaging of upper tracts
- retrograde placement of ureteric stents

What are the advantages of rigid endoscopes?

- better optics
- larger working channels
- improved visualization from better water inflow
- easy manipulation

What are the advantages of flexible endoscopes?

- greater comfort
- patient can stay in supine position and avoid lithotomy
- easier to overcome high BN
- better able to inspect at any angle

RETROGRADE PYELOGRAPHY

List some of the indications for retrograde pyelography.

- less common now with CT urogram
- hematuria
- persistent filling defects of ureter or renal collecting system
- unexplained +ve urine cytology
- hydronephrosis
- ureteric obstructions (eg stones, UPJO, etc)
- ureteric fistulas

What are the important steps of a retrograde pyelogram?

- take scout film before contrast injection
- flush air bubbles out of ureteral catheter
- gentle insertion of ureteral catheter to prevent submucosal undermining/perforation
- collect cytology before injection of contrast (use NS not sterile water)
- delayed films taken

List DDx for filling defect on retrograde pyelogram.

- “U CANT See Fungus Polyp”
- Ureteritis cystica
- Clot
- Air bubble
- Necrotic papilla
- Tumour
- Stone (radiolucent)
- Fungus Ball
- Polyp

Chapter #7 – Laparoscopic Surgery

IN THE O.R.

Which instruments must be checked prior to starting a lap surgical case?

- irrigation-suction
- cautery unit
- CO2 tank
- camera (white balance and light source)
- insufflation flow
- Veress needle flow and proper tip retraction
- have open laparotomy set ready

PERFORMING THE PROCEDURE

What are the different gas insufflants used to create pneumoperitoneum?

- 1) CO2 } **not combustible & very soluble in blood (rapid reabsorption)**
 } may cause acidosis and be an issue in pts with severe chronic respiratory disease
- 2) Helium } **inert gas that is not combustible & not an issue for respiratory pts**
 } not very soluble in blood (higher gas embolism rate)
- 3) Nitric oxide } combustible
- 4) room air } combustible & not very soluble

What are the advantages of CO2 in laparoscopy?

- cheap
- rapid reabsorption
- non-flammable
- colourless
- odourless
- non-toxic } no harm to OR staff

What insufflator readings suggest successful pneumoperitoneum?

- 3 consecutive readings of low pressure (<10mmHg)
- high flow readings throughout

What are the advantages of placing the initial trocar in the umbilical area?

- abdo wall is thinnest
- good post-op cosmesis

What are the disadvantages of placing the initial trocar in the umbilical area?

- potential injury to nearby L common iliac, aorta, or IVC
- umbilicus lies above bifurcation of aorta } angle toward pelvis after going through fascia
 } less angulation needed in obese patients b/c umbilicus usually more caudad

What are the other potential initial trocar sites?

- 2 fingerbreadths medial & 2 fingerbreadths superior to the ASIS } when in lateral decubitus
- Palmer's point } midclavicular line on subcostal margin on right (for lateral decubitus)

What are the different methods to gain access into the peritoneum?

- 1) Veress needle
 - 2) open Hasson-technique
 - 3) Blind trocar insertion (mainly gyne)
 - 4) hand-port access } usually better if made after pneumo developed (fascia on stretch)
 - 5) visual-trocar (eg Visi-port)
- ➔ **need to close ports ≥10mm } no need to close 5mm or self-dilating ports (except in kids)**

What are the different ways to check proper placement of a Veress needle?

- [illegible]

What are the different methods to gain access to the extraperitoneal space?

- [illegible]

What types of trocars are available for use in laparoscopic surgery?

- disposable and nondisposable
 - 3-20mm diameter
 - 5-15cm length
 - bladed (+/- guarded) or dilating trocars
- 10-fold lower rate of hernia and epigastric vessel injury with dilating trocars**

What types of hand ports are available for use in laparoscopic surgery?

- Gelport (Applied Medical) → SMH
→ only one that doesn't lose pneumo with removal of hand
- Omniport (Advanced Surgical Concepts)
- LapDisc (Ethicon)

What other types of energy modalities are used for cutting and hemostasis?

- ligasure } bipolar radiofrequency seals 5mm vessels
- harmonic (U/S) } not good for vessels
- argon beam } must be vented to prevent high pressures

What surgical pharmaceuticals are used as topical hemostatics, sealants, and glues?

- Tisseel } fibrin glue (**fibrinogen & thrombin**)
 - } hemostatic and adhesive
 - } takes ~20mins to prepare and contains bovine components
- Floseal } **thrombin-soaked** oxidized cellulose particles
 - } hemostatic but NOT adhesive
 - } takes only 2mins to prepare and works with oozing
- BioGlue } bovine serum **albumin & glutaraldehyde**
 - } adhesive
 - } no preparation but must be applied to dry surface only

Which port sites need to be closed?

- bladed/cutting trocars } all sites >5mm
- dilating trocars } may not need to close even 12mm ports
- } significantly less abdo wall bleeding and port site hernias
- hand ports } should always be closed first

PHYSIOLOGIC CONSIDERATIONS IN THE ADULT

What are the main physiologic effects of a pneumoperitoneum?

- 1) Cardiovascular
 - ↓'d CVP if pt has low atrial pressures } ↑'d CVP if pt has high atrial pressures (hypervolemic), but ↓'d once ≥ 20 mmHg
 - ↑'d MAP
 - ↑'d CO at ~ 10 mmHg but CO ↓'s when ≥ 20 mmHg (decreased venous return)
 - ↑'d SVR
 - tachycardia (hypercarbia stimulates sympathetics)
 - arrhythmias (ventricular extrasystoles from hypercarbia)
 - **bradyarrhythmias from vagal stimulation during initiation of pneumo**
 - **dramatic hypoTN can occur upon insufflation (vaso-vagal response of pneumo)**
 - Rx - desufflate and remove Trendelenburg
- 2) Respiratory
 - ↑'d peak airway pressures
 - ↓'d FRC and TLC
 - ↓'d vital capacity due to Trendelenburg and pneumo
 - ↑'d pCO₂
- 3) Renal
 - ↓'d GFR at pressure ≥ 10 mmHg
 - **oliguria from decreased renal vein blood flow & direct renal parenchymal compression at pressures > 10 mmHg**
 - use of lasix, mannitol, IVF can decrease oliguria
- 4) Bowel
 - ↓'d mesenteric blood flow } rarely results in mesenteric thrombosis
 - less post-op ileus
- 5) Acid-Base status
 - hypercarbia
 - respiratory acidosis
- 6) Hormonal
 - less hepatic stress response than open surgery
 - less catabolic cytokine and opioid release than open surgery
- 7) Immunologic
 - less immunosuppression than open surgery
 - less tumour cell growth after lap surgery

At what pressures do you start to see specific physiologic changes?

- HR ↑'s until 40mmHg, then pressure causes HR to ↓
 - HR may initially decrease from vagal stimulation at very start of case
- GFR & urine output decreases at pressures > 10 mmHg
- PCO₂ only increases at pressures > 10 mmHg

List complications of CO₂ pneumoperitoneum at 15cm H₂O.

- "MR CHAOS BP"
- Mesenteric ischemia
- Respiratory acidosis
- CO₂ embolus
- Hypercapnia
- Arrhythmias
- Oliguria
- Subcutaneous emphysema
- Barotrauma
- Pneumothorax, pneumomediastinum, pneumopericardium

What are the advantages & disadvantages of the different insufflants used in laparoscopy?

	ADVANTAGES	DISADVANTAGES
CO₂	<ul style="list-style-type: none"> - noncombustible - cheap - quickly reabsorbed & very soluble in water (less chance of air embolus) - no harm to OR staff members - odorless 	<ul style="list-style-type: none"> - hypercarbia due to high solubility may lead to cardiac arrhythmias, increased HR, increased cardiac contractility
Nitrous	<ul style="list-style-type: none"> - less peritoneal irritation - fewer acid-base changes - less arrhythmias 	<ul style="list-style-type: none"> - reduced cardiac output - increased MAP, HR, and CVP Oxide - combustible - bowel distension
Helium	<ul style="list-style-type: none"> - noncombustible - no hypercarbia so better for COPD pts - may decrease tumour cell growth - can be used w/ local & regional anesthetic - less peritoneal irritation 	<ul style="list-style-type: none"> - less soluble so higher risk of air embolism - expensive

TROUBLESHOOTING

What are the potential major complications of transperitoneal laparoscopic surgery (CHART)?

- abdominal sx } overall ~15%
 - } post-op complications more common than intra-op (7.5% vs 5.7%)
 - } vascular injuries the most common complications (~3%)
- pelvic sx } overall ~23%
 - } post-op complications more common than intra-op (20% vs 4%)
 - } bowel injuries the most common complications (1.2%)

What are the potential complications of gaining access with the Veress needle?

- preperitoneal placement } early high pressures + uneven distension of the abdomen
- vascular injuries } blood in the needle
 - } suspect retroperitoneal bleed if patient becomes unstable & there is a "loss" of working space within the abdomen
 - use of blunt trocars decreases incidence of epigastric vessel injury 5-fold
- visceral injuries } blood, urine, bowel content on aspiration
 - } argon laser for liver or spleen
 - } needle withdrawal sufficient for bowel or bladder injury

What are signs of bowel insufflation?

- asymmetrical abdominal distension
- flatus
- **high pressures after <2L of insufflation**
- aspiration of bowel content

What is the management of bowel insufflation?

- stop insufflation
- withdraw needle
- use open access technique at different site

List clinical signs of gas embolism?

- often due to puncture of blood vessel or organ with Veress needle or large open veins
- acute CV collapse
- cyanosis
- sudden decline in O₂ sat's (hypoxia)
- arrhythmias
- initial increase followed by marked decrease in end-tidal CO₂
- "mill-wheel" murmur
- pulmonary edema
- foaming of blood sample drawn by anesthesia

What is the management of gas embolism?

- communicate with anesthesia
- immediate stoppage of insufflation + desufflation of abdomen
- LLD (right-side up) + Trendelenburg } to minimize R ventricle outflow problems
- hyperventilate with 100% O₂
- advance central line into right heart and try to aspirate } rarely successful
- hyperbaric O₂ & cardiopulmonary bypass reported

What is the management of barotrauma?

- from pressures that are too high (watch out for argon beam laser)
- presents w/ hypoTN from decreased CO secondary to acute drop in venous return
- may also present as a pneumothorax or pneumomediastinum from high ventilation pressures
- more common with retroperitoneal lap surgery

Rx → desufflate abdomen

→ once stable, reinsufflate to 10mmHg only

What are the RFs for subcutaneous emphysema from lap surgery?

- 1) large port site incisions
 - 2) lengthy procedure
 - 3) use of high intra-abdominal pressures
- more common in retroperitoneoscopy

What are the potential complications assoc'd w/ the "blind" placement of 1st trocar after Veress needle access?

- bowel perforation } if through-and-through, may not notice until after placement of 2nd port
Rx → lap repair if skilled, otherwise open repair
→ triple Abx
- vascular injury } aggressive insertion with bladed trocar
} most commonly aorta, common iliac arteries, mesenteric vessels, or epigastrics
Rx → close trocar and leave in place, call trauma/vascular sx, open abdomen, locate and control bleeding
→ if skilled and it is a controlled hemorrhage, may attempt lap repair
- bladder injury } usually during gyne surgery → less common now with blunt trocars
Rx → should be repaired lap or open and NOT left to heal with prolonged Foley

What are some potential complications associated with placement of secondary trocars?

- abdo wall vessel injury } blood dripping down trocar is early sign
Rx → locate vessel by cantilevering trocar into 4 quadrants and seeing which position tamponades bleeding
→ can use 'hot' curved scissors, Keith needle + bolster on abdominal surface, Carter-Thomason, Foley balloon
- poor trocar placement } can lead to 'crossing swords' and 'rollover'

What conditions related to lap surgery can lead to ARRHYTHMIAS?

- CO2 insufflation
- hypercapnia
- increased vagal tone from traction on pelvic or peritoneal structures
- Trendelenburg
- certain anesthetic agents (eg halothane)
- endobronchial intubation
- gas embolism
- pre-op anxiety

What is the most common arrhythmia associated with lap surgery?

- sinus tachycardia

What are the ways to decrease HYPERCAPNIA?

- increase ventilatory rate and tidal volume } blow it off
- use of PEEP
- reduction of pneumoperitoneal pressure
- switch to Helium insufflant

What are the ways to prevent post-op ASPIRATION?

- iv metaclopramide 10mg (increases LES tone)
- avoid atropine if possible (decreases LES tone)
- H2 blockers reduce acidity
- use of cuffed ETT

What are the clinical effects of HYPOTHERMIA?

- increased bleeding tendency (platelet dysfunction, enhanced fibrinolysis)
- increased BP from adrenergic response
- prolonged recovery time
- 2-3fold increase in post-op MIs
- impaired wound healing and increased wound infections

What are the 4 main ways to cause THERMAL BOWEL INJURY during lap surgery?

- ~50% of bowel injuries are due to cautery
- 1) inappropriate direct activation
 - 2) coupling to another instrument
 - 3) capacitive coupling (current passes through intact insulation)
 - 4) insulation failure



→ CAPACITIVE COUPLING

What is the post-op management of a BOWEL INJURY after lap surgery?

- **often presents late (usually after discharge)**
- often see **distension + low-grade fever**
- **uncommon to have peritonitis or ileus**
- **leukopenia (with left shift) and single trocar site pain } suggestive of bowel injury**

Rx → if minor and discovered late (>5-7days) then can try conservative mgt with NPO, TPN, ABx
→ if major or patient fails conservative management, will need open repair
→ bowel resection w/ 6cm margin on either side of necrotic area recommended for monopolar injuries

What are the intra-op management options for VASCULAR INJURY during lap surgery?

- increase pneumo
- liberal use of irrigation/suction
- place gauze sponge into abdomen via 12mm port
- place extra 5mm port to use grasper to help
- if skilled can attempt lap repair, otherwise open repair } hand-assisted approach also option
- call vascular or trauma surgery if major injury

What are the management options for BLADDER INJURY after lap surgery?

- intra-op } pneumaturia or hematuria, clear fluid welling up in pelvis
Rx → lap repair with absorbable suture
→ open repair if extensive
- post-op } hematuria, oliguria, urinary ascites, mild elevation of creatinine, hypoNa, fever, S/P tenderness, vaginal discharge
Rx → treat like bladder trauma (extraperitoneal vs intraperitoneal)

What are the management options for URETERIC INJURY after lap surgery?

- often not detected intra-op
Rx → repair over stent if due to mechanical trauma
→ formal resection & repair over stent if thermal injury } location dictates type of repair
- usually diagnosed post-op } abdo/flank pain, fever, signs of focal peritonitis, leukocytosis, ileus, urinary ascites, urinary fistula
Rx → Foley + stent } remove foley once cystogram shows reflux without extravasation
} stent for 6-8 weeks followed by imaging to r/o stricture development
→ if unable to pass stent, will need NT + repair } endourologic vs open repair

What are the management options for PANCREATIC INJURY after lap surgery?

- often due to mechanical retraction } 2% after left Nx, 9% after left adrenalectomy
- rare to be noticed intra-op
Rx → gen sx consult
→ mobilize tail and use endo-GIA
- usually diagnosed post-op (75%) } abdo pain, elevated lipase/amylase, leukocytosis
Rx → NG, NPO, TPN
→ perc drainage of collection } remove once <50cc/24hrs
→ low fat diet started once healed

What are the management options for SPLENIC INJURY after lap surgery?

- surgical
- Floseal
- argon beam laser
- splenectomy

What are the potential nerve injuries suffered after lap surgery?

A) positioning-related

- get pain, parasthesia, weakness of muscles

1) **brachial plexus** } **most commonly injured**

} often from ABduction of arm >90 degrees, extreme outward rotation of head of humerus, or compression during Trendelenburg

2) femoral nerve } from extreme lateral rotation and ABduction of hip

3) sciatic nerve } from stretching of superior leg during lateral decubitus position

Rx → usually noticed only post-op

→ needs neuro consult, physio, etc

B) mechanical injury

1) obturator nerve } most commonly injured nerve due to mechanical forces

} can't ADduct the ipsilateral leg

2) genitofemoral nerve } often during radical Nx or NephroU

} numbness to scrotum/labia majora/mons + upper thigh

Rx → if noticed intra-op, plastics consult for possible repair with 6-0

→ if post-op, need neuro consult, physio, etc

What is the management of post-op RHABDOMYOLYSIS?

- usually associated with prolonged lap surgery involving a kidney rest in M patients
- should use gel or foam (avoid egg crates) and avoid the use of a kidney rest
- brown urine, severe pain, elevated serum creatine phosphokinase

Rx → hydration & alkalinization

→ physio for long-term disability associated with muscle necrosis

What is the management for LYMPHOCELE formation post-lap surgery?

- often presents late (3wks +) as painful mass but may also lead to lower extremity edema +/- DVT/PE

Rx → perc drainage

→ sclerosant therapy eg tetracycline

→ transperitoneal lap marsupialization

What is the management of CHYLOUS ASCITES?

- often presents late with no associated pain, fever, or bowel dysfunction
- usually after L-sided retroperitoneal surgery (supra-hilar dissection)

Rx → send ascitic fluid for culture, CBC, triglycerides, cholesterol, and lytes

- **chylous ascites if high lymphocytes, cholesterol, and triglycerides**

→ low-fat, medium-chain triglyceride diet } usually self-limited

→ somatostatin

→ open or lap surgery } give fatty TPN load and look for white lymphatic fluid from site of injury

What are the potential complications of renal tumour ablation?

→ minor

- elevated creatinine
- hematuria
- minor hemorrhage (small perinephric hematoma)
- pain or paresthesia at the probe site
- UTI
- wound infection
- liver burn/freeze

→ major

- bowel injury
- ileus
- open conversion
- significant hemorrhage (large or expanding hematoma)
- urinary extravasation
- UPJO

TRANSPERITONEAL VS EXTRAPERITONEAL APPROACHES

What are the advantages & disadvantages of transperitoneal vs retroperitoneal Lap surgery?

	ADVANTAGES	DISADVANTAGES
Transperitoneal	<ul style="list-style-type: none">- easier- more working space- better for pelvic surgery	<ul style="list-style-type: none">- higher risk of intra-peritoneal organ injury- may need more Trendelenburg- previous abdo sx may preclude
Retroperitoneal	<ul style="list-style-type: none">- lower risk of bowel injury & post-op ileus- very low risk of trocar site hernia- can avoid hostile abdomen- rapid & direct access to renal hilum- less risk of contaminating peritoneum from renal pathology (urine, infection, tumour)	<ul style="list-style-type: none">- less working space- more pulmonary complications eg pneumothorax

Chapter #8 – GU Infections

DEFINITIONS

Define the common terms used to describe GU infections?

- 1) UTI → inflammatory response of urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria
- 2) bacteriuria → presence of bacteria in the urine, which is normally free of bacteria
→ bacteria may be in urothelium without bacteriuria and alternatively, bacteriuria may represent bacterial contamination of a sterile specimen
→ S/P aspiration is most reliable specimen, then catheterized, then voided
→ symptomatic vs asymptomatic bacteriuria
- 3) pyuria → presence of WBCs in the urine; generally indicative of infection & an inflammatory response of the urothelium to bacterium
→ **bacteriuria w/o pyuria indicates colonization without infection**
→ **pyuria w/o bacteriuria (sterile pyuria) may indicate TB, stones, cancer, etc**
- 4) cystitis → describes clinical syndrome of dysuria, frequency, urgency, and occasionally S/P pain
→ may also be associated with infection of urethra, vagina, or other noninfectious conditions such as IC, bladder carcinoma, or stones
- 5) acute pyelonephritis → clinical syndrome of fever, chills, and flank pain that is accompanied by bacteriuria and pyuria
→ may be difficult to diagnose in patients with SCI and the elderly
- 6) chronic pyelo → describes a shrunken, scarred kidney, that is post-infectious but is frequently not associated with UTI
→ may cause **focal, coarse scar in renal cortex overlying a calyx**, almost always accompanied by some calyceal distortion
→ less commonly, renal scarring from infection can result in atrophic pyelonephritis or generalized thinning of the renal cortex
- 7) uncomplicated UTI → describes an infection in a healthy patient with a structurally & functionally normal urinary tract
→ infection usually easily eradicated
- 8) complicated UTI → infection that is associated with factors that increase the chance of acquiring bacteria and decrease the efficacy of therapy
→ “ACADEMIC WHIP”
- 9) first or isolated infection → patient has never had a UTI or has one remote from previous
- 10) unresolved UTI → has not responded to ABx
- 11) recurrent UTI → **occurs after documented resolution of an antecedent infection**
- 12) reinfection → new event associated w/ reintroduction of bacteria from outside GU tract
- 13) bacterial persistence/relapse → recurrent UTI from same bacteria reemerging from a focus within the GU tract (eg stone)
- 14) prophylactic antimicrobial therapy → prevention of reinfection of urinary tract by the use of ABx
- 15) suppressive antimicrobial therapy → suppression of a focus of bacterial persistence that can't be eradicated

- 1) obligate intracellular bacteria
 - Chlamydia trachomatis, Rickettsia rickettsiae, Coxiella burnetii
- 2) extracellular bacteria
 - NO CELL WALL
 - Mycoplasma pneumonia
 - CELL WALL
 - GRAM +VE
 - GP cocci
 - Staphylococcus } coag +ve (S. aureus)
 - (clusters) } coag -ve (S. epidermidis, S. saprophyticus)
 - Streptococcus } β hemolytic (GAS – S. pyogenes)
 - (chains) } α hemolysis (S. viridans)
 - Enterococcus (E. faecalis)
 - GP bacilli
 - Clostridium } C. difficile, C. botulinum, C. tetani, C. perfringens
 - Bacillus anthracis
 - Corynebacterium diphtheriae
 - Listeria monocytogenes
 - GRAM -VE
 - GN cocci
 - Neisseria } N. gonorrhea, N. meningitidis
 - Moraxella
 - GN bacilli
 - Enterobacteriaceae } Escherichia coli
 - } Klebsiella pneumoniae
 - } Enterobacter
 - } Proteus mirabilis
 - } Salmonella typhi
 - Pseudomonas aeruginosa
 - Helicobacter pylori
 - Haemophilus ducreyi (chancroid)
 - Bacteroides fragilis
- 3) atypicals
 - acid-fast gram +
 - Mycoplasma tuberculosis (TB)
 - spirochetes
 - Treponema pallidum (syphilis)
 - Borrelia burgdorferi (Lyme disease)

- **AbN** or anomalous GU tract } calyceal diverticulum, bladder diverticulum, neurogenic bladder, etc
- **Children**
- **ABx** use (recent)
- **DM**
- **Elderly**
- **Male**
- **Immunosuppression**
- **Catheterized**
- **Week-long** symptoms at presentation (7days)
- **Hospital-acquired**
- **Instrumentation** (recent)
- **Pregnancy**

INCIDENCE AND EPIDEMIOLOGY

How common are UTIs?

- most common bacterial infection } 1.2% of all F office visits, 0.6% of all M office visits
- **prevalence much higher in F but with increasing age, the ratio decreases**
- nearly 30% of F have symptomatic UTI by age 24, almost 50% during their lifetime
- incidence increases with institutionalization/hospitalization and concurrent disease
- **increased incidence with pregnancy, SCI, DM, MS, HIV/AIDS & previous UTI**
- **usually recurrent reinfection NOT relapse**
- most reinfections occur in clusters and occur ~2 weeks apart
- Abx therapy and prophylactic Abx's reduce morbidity and reinfections but do not alter the underlying predisposition to recurring infections

What is the long term sequelae of UTIs?

- uncomplicated } unknown, but no association with renal scarring, HTN, or ESRD
- complicated } can lead to ESRD and HTN

PATHOGENESIS

What are the factors associated with successful infection of the GU tract?

- | | | |
|---|---|-----------------------------------|
| 1) virulence factors (eg hemolysin, type 1 pili, P pili, etc) | \ | - ↑'d virulence req'd to overcome |
| 2) inoculum size | } | strong host resistance & minimal |
| 3) inadequacy of host defense mechanisms | / | virulence able to overcome |
| | | significantly compromised host |

What are the routes of infection of the GU tract?

- 1) ascending route → **most UTIs are from ascent of GI bacteria through urethra**
 - adherence of pathogen to introital & urothelial mucosa plays a big role
 - most episodes of pyelo are from ascent of bacteria from bladder
 - 1° VUR not necessary } UVJ edema from cystitis may induce VUR
 - any process that decreases ureteral peristalsis increases risk of pyelo (eg pregnancy, obstruction, gram -ve endotoxins)
- 2) hematogenous route → uncommon in normal individuals
 - 2° infection of kidney from *S. aureus* bacteremia or *Candida fungemi*
- 3) lymphatic route → rarely can see direct extension of bacteria from adjacent organs via lymphatics (eg bowel infection, retroperitoneal abscess)

What are the common urinary pathogens that cause UTIs?

- most commonly from facultative aerobes originating from bowel flora
- can get infections from flora of vagina or perineal skin } eg *Staph epidermidis* or *Candida albicans*
- **most common cause by far is E coli**
- community-acquired
 - *E coli* (85%)
 - other gram negatives } *Proteus*, *Klebsiella*,
 - gram positives } *E. faecalis*, *S. saprophyticus* (usually females)
- nosocomial infections
 - *E coli* (50%)
 - *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Pseudomonas*, *Providencia*, *E faecalis*, *S epidermidis* (females)
- less common organisms include *Gardnerella vaginalis*, *Mycoplasma* species, & *Ureaplasma urealyticum*
- anaerobic organisms less common overall but often found in suppurative infections such as scrotal abscess, prostatic abscess, perinephric abscess
 - *Bacteroides*, *Clostridium perfringens*

What is the significance of *M. tuberculosis* in the GU tract?

- found on acid-fast cultures NOT under routine aerobic cultures } often associated w/ **sterile pyuria**
- presence of mycobacteria may not indicate tissue infection

What are the indications to treat GU tract TB?

- symptoms
- abN urine sediment
- presence of granulomas
- endoscopic or radiologic evidence of infection
- absence of other pathogens
- repeated demonstration of *M. tuberculosis*

List the potential causes of sterile pyuria

→ INFECTIOUS

- GU TB
- UTI with fastidious organism
- UTI but on ABx
- class 3 chronic prostatitis
- parasitic infections
- Chlamydia urethritis
- adjacent appendicitis

→ NON-INFECTIOUS

- stones
- tumour
- GU sarcoidosis
- renal papillary necrosis
- PCKD
- AIN
- post-RADs cystitis
- post-cyclophosphamide cystitis
- interstitial cystitis

What bacterial virulence characteristics play a role in UTIs?

- genes for putative chaperone-usher systems
- autotransporter proteins that may function as adhesins, toxins, proteases, invasins, serum resistance factors, or motility mediators
 - **Sat** is an autotransporter that is toxic to urinary tract cells
 - **hemolysin** HlyA forms pores in host cell membranes
- production of acid polysaccharide capsule that protects bacteria from phagocytosis by human leukocytes

What is the role of bacterial adhesins that allow attachment to urinary tract tissues?

- fimbrial or afimbrial (pilus) adhesins expressed by bacteria
- type 1 pili } facilitates bacterial colonization of vaginal mucosa & bladder
 - } mediate hemagglutination of erythrocytes (inhibited by mannose)
 - } helical rod composed of repeating FimA and FimH subunits
 - } **interaction of FimH and receptors on surface of bladder epithelium (uropilins) are critical for bacterial colonization & infection**
- P pili } facilitates bacterial adherence to kidney
 - } mediate hemagglutination of erythrocytes (resistant to mannose)
 - } not associated with renal scarring or reflux
- S pili } bind to bladder and kidney epithelial cells via the SfaS adhesin
- depending on environmental growth conditions, bacteria can produce rapid changes in pilus expression } pilated phase and nonpilated phases
- phase variation seen in vivo } generally more pilated bacteria in bladder & less pilated bacteria in kidney
 - } **more type 1 pili in bladder, more P pili in kidney**

What is the significance of epithelial cell receptivity in recurrent UTIs (*E. coli*)?

- ↑'d adherence of pathogenic bacteria to vaginal epithelial cells seen in F susceptible to UTIs → **HLA-A3 genotype may be a major susceptibility factor in UTIs**
- ↑'d adherence also seen of buccal epithelial cells
- ↑'d bacterial adherence during early phase of menstrual cycle & in postmenopausal F (↓'d estrogen)
- ↑'d epithelial receptivity for bacteria in women with Lewis Le (a-b-) and Le(a+b-)
- vaginal fluid may influence bacterial adherence (may be IgA protein related)

What features of biofilm shield bacteria from environmental challenges?

- slower growth rate of bacteria (>60 minutes)
- expression of factors that inhibit antimicrobial activity
- inability of antimicrobial agent to penetrate biofilm matrix

Which microorganisms of the introitus, periurethral area & urethra form a barrier against uropathogens?

→ host defences

- lactobacilli
- coagulase –ve staphylococci
- corynebacteria
- streptococci

\
/
/

use of ABx and spermicidals
may change normal flora

What bacterial virulence factors exist that increase the likelihood of UTIs?

→ “**Hokus-POKEUS**”

- **H**emolysin & mannose-resistant **H**emagglutination (MRHA)
- **P**ili or fimbriae (type 1 pili, P pili, P fimbriae)
- **O** antigen (cell wall)
- **K** antigen
- **E**xotoxin production
- **U**rease production
- **S**iderophore production

What host/urinary defence factors inhibit bacterial growth? }} “LOCAL Grown STUUF”

- | | |
|--|--|
| - L actobacillus | - S alts (high) |
| - O rganic acids (high) | - T amm-Horsfall proteins (inhibits type 1 pili) |
| - C ytokines & PMNs | - U mbrella cell shedding |
| - A cidic urine pH | - U rea (high) |
| - L actoferrin (scavenges essential Fe) | - F low of dilute urine (most important) |
| - G lucose (low) | |

What factors are involved in pathogen recognition in the GU tract?

- host recognition of pathogen mediated by pathogen-associated molecular pattern receptors (PAMPs) such as Toll-like receptors (TLR4 and TLR11)
- innate immune response occurs faster than adaptive response
- innate immune response involves:
 - PMN leukocytes
 - **neutrophils → essential for bacterial clearance**
 - macrophages
 - eosinophils
 - NK cells
 - mast cells
 - dendritic cells
- adaptive response involves specific recognition of pathogen by T & B lymphocytes and occurs 7-10 days after infection

What is the significance of induced exfoliation?

- exfoliation & excretion of infected and damaged superficial cells (mediated by type 1 pillated bacteria) is important in clearing UTI
- some bacteria can suppress immune cells, increase apoptosis of immune cells, and decrease the inflammatory response leading to bacterial invasion into deeper tissues

What factors can alter host defense mechanisms and increase the risk of UTIs?

- obstruction → urine stasis increases bacterial growth and adherence to urothelial cells
→ stasis itself is not predisposing factor } needs inoculum of bacteria
- VUR → unclear as to whether it is a predisposing factor } does increase risk of pyelonephritis
- systemic diseases that result in papillary damage
 - DM, sickle cell, adult nephrocalcinosis, hyperPO₄, hypoK, analgesic abuse, gout, sulfonamide nephropathy, heavy-metal poisoning, aging
 - UTIs more severe in DM, more common in female DM only, pyelo more common in all DM
- HTN
- vascular obstruction
- HIV
- pregnancy → ~5% have bacteriuria & ~25-35% with untreated bacteriuria get acute pyelonephritis
- SCI → highest severity and morbidity of UTIs
 - bladder overactivity or flaccidity complicates UTIs
 - often also see stones, reflux, hydronephrosis

How does renal papillary necrosis present?

- acute fulminating illness with rapid progression OR chronic disease with incidental finding on IVP or retrograde
- some may pass necrotic papillae, some may never pass necrotic tissue
 - retained necrotic papillae may calcify (especially in association with infection)
- may see various degrees of renal involvement
 - medullary or papillary changes
 - irregular sinuses
 - medullary cavities
 - classic ring shadows
- early diagnosis is important!!! } improves prognosis & reduces morbidity

List conditions associated with renal papillary necrosis (CHART). } } } POST CCAARRDD

- | | |
|------------------|-------------------------|
| - Pyelonephritis | - Cirrhosis |
| - Obstruction | - Candidiasis (renal) |
| - Sick cell | - Analgesic abuse |
| - TB | - Amyloidosis |
| | - Rejection of renal Tx |
| | - Renal vein thrombosis |
| | - DM |
| | - Dehydration |

→ other } cryoglobulinemia, contrast use, calyceal arteritis, necrotizing angitis, acute pancreatitis, shock

List GU manifestations of sickle cell disease/trait. (AUA Update #18 – '05)

→ HUGE F'N PRIAPISM

- Hematuria (dysmorphic RBCs) } M > F and L side 4x more than R
- UTIs
- Glomerular disease (MPGN, immune complex GN, etc) } leads to proteinuria
- ED
- Frequency, polyuria, etc (Nephrogenic DI)
- Nocturnal enuresis
- Priapism
- RTA (distal)
- Infertility
- ARF
- Papillary necrosis
- Infarcts (renal medulla, testicular)
- Slow (chronic) renal failure
- Medullary RCC (trait)

CLINICAL MANIFESTATIONS

What are the signs and symptoms of UTI?

- cystitis } dysuria, frequency, urgency, S/P pain, hematuria
- pyelonephritis } fever, chills, flank pain, N/V
 - } renal or perirenal abscess may cause indolent fever and flank mass/pain

What are the causes of a false-negative urinalysis or culture?

- early in an infection when numbers of bacteria and WBCs are low or diluted by increased fluid intake
- occasionally can be low even despite colonization and inflammation of urothelium

What is the most accurate way to obtain a urine sample free of contamination?

- 1) S/P aspiration } 5cc for culture and 15cc for u/a
- 2) catheterized specimen
- 3) voided specimen (MSU) } prep if uncx'd or female
 - epithelial cells or lactobacilli on u/a may indicate contamination

What is the risk of catheter-induced UTI?

- varies based on patient population } 1% in non-hospitalized, healthy patients
 - } 20% in hospitalized women
- can prevent catheter-induced UTI by single dose of Abx (eg Septra) } ONLY recommended in high-risk patients

What are the findings indicative of a UTI on microscopic u/a?

- 10cc of urine centrifuged for 5min at ~2000 rpm
- **bacteriuria is found in >90% of infections } >105 cfu/mL**
 - can have +ve C&S but -ve u/a } bacterial count <30,000/mL may not be detected
 - if u/a shows bacteria but C&S is negative may be normal flora
- **>2 WBC per HPF is suggestive of infection** } could also be inflammation from eg TB, stones, GN
- microscopic hematuria found in ~50% of UTIs
- microscopic hematuria + bacteriuria is very specific for UTI but has low sensitivity
- presence of nitrates has good specificity but low sensitivity
- **if squamous epithelial cells present on u/a, consider contamination**

What is the problem with using 105 cfu/mL as defining a UTI?

- 1) ~30% of women with symptomatic UTIs have bacterial counts between 10² and 10⁴ cfu/mL
 - from slow doubling time (q30-45min) and frequent voiding (q30min)
 - **in symptomatic pts, 10² cfu/mL should be threshold value for defining significant bacteriuria**
- 2) contamination may account for the 10⁵ cfu/mL

What are the 2 different techniques used for urine C&S?

- 1) direct surface plating on split-agar → 1/2 blood agar (Gram +ve & -ve) and 1/2 EMB (Gram -ve only)
 - refrigerate specimen and culture within 24hrs
- 2) dip slides → one side soy agar (grows all bacteria) and the other is EMB (Gram -ve only)
 - no need for refrigeration

What are the benefits of ureteral catheterization?

- separation of bacterial persistence into upper & lower urinary tracts
- separation of infection between one side & the other
- localization to ectopic ureters or nonrefluxing ureteral stumps

What is the distribution of localized sources of infection in most UTIs?

- **~50% in bladder**
- ~25% bilateral renal
- ~25% unilateral renal

IMAGING TECHNIQUES

What are the indications for imaging studies in patients with UTIs?

- in men
- in compromised host
- febrile infections
- signs or symptoms of urinary tract obstruction
- failure to respond to Abx
- pattern of recurrent infections

What are the indications for imaging studies for acute pyelonephritis (CHART)?

- “Pyelo Probably SOUNDS Refractory”
- Papillary necrosis (sickle cell anemia, severe DM, analgesic abuse)
- PCKD and ESRD
- Stone history (especially struvite)
- Obstruction possible (stone, tumour, stricture)
- Unusual infecting organisms (TB, fungus, urea-splitting bacteria)
 - must r/o strictures, fungus balls, stones
- Neurogenic bladder
- DM → may get emphysematous pyelo, papillary necrosis, ureteral obstruction from sloughed papillae
 - prone to developing perinephric abscesses
- Surgery that predisposes to stricture (diversion, reimplant, ureteroscopy)
- Refractory to appropriate Abx (after 5-6 days)
 - must r/o perinephric or renal abscesses

What are the correctable causes of bacterial persistence (CHART)?

→ **recall, reinfection UTI more common than persistent/relapsing UTI**

→ “PUFFED UP MASK”

- | | |
|--|--|
| - Papillary necrosis | - Ureteral stump (infected post Nx) |
| - Urachal cyst (infected) | - Prostatitis (chronic bacterial) |
| - FB | - MSK |
| - Fistulae (enterovesical, rectourethral, VVF) | - Abscess (perivesical, perinephric) |
| - Ectopic ureter | - Stones (infected) } most common |
| - Diverticulum (urethral) | - Kidney (atrophic segment) |

What radiologic tests are used to investigate complicated GU infections?

- 1) KUB → radio-opaque stones
 - abN gas pattern in emphysematous pyelo
 - perirenal abscess } absent psoas or abN renal contour
- 2) renal tomograms → shows small or poorly calcified stones despite gas and stool shadows
 - localizes calcifications or gas to the kidney
- 3) IVP → helps identify site of obstruction and duplication anomalies
- 4) VCUG → role in assessing for VUR in patients w/ neurogenic bladders, F with urethral diverticulum
- 5) U/S → **noninvasive, easy, fast, no radiation or contrast**
 - **good 1st line test for stones, hydro, pyonephrosis, perirenal abscesses & PVR**
 - should also have KUB
- 6) CT or MRI → best anatomic detail on cause, site, and extent of infection
 - can also guide therapy eg for perc drainage of abscess
- 7) renal scans → can detect decreased renal perfusion in acute renal infections

PRINCIPLES OF ANTIMICROBIAL THERAPY

Classify the different Antibiotic drugs.

- Beta-Lactams } inhibits cell wall synthesis (**bactericidal**)
 - penicillins (eg. pen G, ampicillin, amoxicillin, piperacillin)
 - cephalosporins (1st gen – cefazolin, cephalexin; 2nd gen – cefuroxime; 3rd gen – ceftazidime, ceftriaxone, cefixime; 4th gen – cefepime)
 - carbapenems (eg imipenem, meropenem)
- Glycopeptides } inhibits cell wall synthesis
 - vancomycin
- Macrolides } inhibits protein synthesis (ribosomal 50S)
 - erythromycin, clarithromycin, azithromycin
- Lincosamides } inhibits protein synthesis (ribosomal 50S)
 - clindamycin
- TMP-SMX } folic acid antagonist (**bactericidal**)
- tetracyclines } inhibits protein synthesis (ribosomal 30S)
 - tetracycline, doxycycline
- aminoglycosides } inhibits protein synthesis (ribosomal 30S) (**bactericidal**)
 - gentamicin, tobramycin, amikacin, streptomycin
- quinolones } DNA gyrase inhibitors (**bactericidal**)
 - cipro, levofloxacin, moxifloxacin, norfloxacin, gatifloxacin, nalidixic acid
- nitrofurantoin } damage bacterial DNA (**bactericidal**)
- metronidazole } DNA damaging metabolites (**bactericidal**)

List Abx that are bactericidal } } } “Stronger, Better Mother F’N Abx”

- Septra
- B-Lactams (penicillins, cephalosporins, Carbapenems)
- Metronidazole
- Fluoroquinolones
- Nitrofurantoin
- Aminoglycosides

What are the determining factors of Abx efficacy?

- urinary levels } blood levels important in patients w/ bacteremia & febrile UTIs with parenchymal involvement (eg pyelo and prostatitis)
- duration Abx level remains above minimal inhibitory concentration of infecting organism
- presence of obstruction
- spectrum of activity of Abx against pathogen

Which Abx have high urinary levels?

- cephalexin (98% of dose) – 250mg po qid
- levofloxacin (95%) – 500mg po od
- sulfamethoxazole (95%) – 250mg po qid
- gentamicin (80%) – 1mg/kg im q8h
- nitrofurantoin – 100mg po qid

What is important in the treatment of UTIs in renal failure patients?

- renal-dosing necessary for Abx with renal clearance
- kidneys may not be able to [] Abx in urine } **quinolones BEST in renal failure pts, then TMP-SMX**

Why is there an increasing number of Abx-resistant UTIs?

- 1) changing bacterial characteristics
 - 2) bacterial selection due to increased Abx use
 - 3) societal & technologic changes that enhance transmission of drug resistance
- occurs due to:
- a) inherited chromosomal-mediated resistance
 - eg Proteus and Pseudomonas are always resistant to nitrofurantoin
 - b) acquired chromosomal resistance } occurs ~5-10% of the time
 - can be due to under-dosing or non-compliance
 - selects out pre-existing mutants
 - eg cipro resistant E coli
 - c) extrachromosomal (plasmid)-mediated resistance due to exposure to Abx
 - R-factor resistance occurs in bowel flora
 - NOT seen after quinolone or nitrofurantoin therapy

What patterns of bacterial resistance are seen?

- increased prevalence of resistance to TMP/SMX, ampicillin & cephalothin
- NO increased resistance to nitrofurantoin & cipro
 - **related to R factor resistance**
 - increased resistance of E coli to cipro is seen in hospitalized patients though (105
 - up to 80% resistance on Tx floors
 - previous use of quinolones and presence of urologic dz are strong predictors

What are common Abx used for UTIs?

- TMP/SMX → good except for enterococcus & Pseudomonas
- nitrofurantoin → good except for Pseudomonas & Proteus
 - high urine levels but poor tissue levels
 - good for prophylaxis regimes Minimally alters N vaginal flora
- cephalosporins → safe in pregnancy
 - usually limit their use to iv therapy & complicated infections
- ampicillin/amoxicillin → high resistance rates
 - good for iv pyelo management
- aminoglycosides → synergistic with TMP/SMX or ampicillin
 - once daily dosing is better for peak [] and reduced toxicity
- fluoroquinolones → ideal for empiric Rx
 - good for Pseudomonas, Staph, and Enterobacteriaceae
 - bad for enterococcus
 - antagonistic with nitrofurantoin

Which antibiotics should be avoided during pregnancy?

- fluoroquinolones (cartilage damage in beagle pups)
- tetracyclines (discoloured teeth, bone abN'ities)
- chloramphenicol (grey baby syndrome → hypoTN, hypothermia, CV collapse)
- sulfa } not safe in T1 or T3 (NTDs, kernicterus, hemolytic anemia)
- aminoglycosides (deafness)
- trimethoprim } not safe in T1 (structural defects – folic acid antagonist)
- nitrofurantoin } not safe in T3 (hemolytic anemia)
- ??? erythromycin (maternal cholestatic jaundice) \ recent data suggest
- ??? flagyl (teratogenic) / they are safe

What is the mechanism of action of the common Abx used for UTIs?

Table 8-8 -- Mechanism of Action of Common Antimicrobials Used in the Treatment of UTIs

<i>Drug or Drug Class</i>	<i>Mechanism of Action</i>	<i>Mechanisms of Drug Resistance</i>
β -Lactams (penicillins, cephalosporins, aztreonam)	Inhibition of bacterial cell wall synthesis	Production of β -lactamase
		Alteration in binding site of penicillin-binding protein
		Changes in cell wall porin size (decreased penetration)
Aminoglycosides	Inhibition of ribosomal protein synthesis	Downregulation of drug uptake into bacteria
		Bacterial production of aminoglycoside-modifying enzymes
Quinolones	Inhibition of bacterial DNA gyrase	Mutation in DNA gyrase-binding site
		Changes in cell wall porin size (decreased penetration)
		Active efflux
Nitrofurantoin	Inhibition of several bacterial enzyme systems	Not fully elucidated—develops slowly with prolonged exposure
Trimethoprim-sulfamethoxazole	Antagonism of bacterial folate metabolism	Draws folate from environment (enterococci)
Vancomycin	Inhibition of bacterial cell wall synthesis (at different point than β -lactams)	Enzymatic alteration of peptidoglycan target

What are the common Abx used to treat UTIs and list their side effects?

Antibiotic agent	Side effects	Contraindications
Amoxicillin or ampicillin	Hypersensitivity, diarrhea, C diff, maculopapular rash	Increased risk of rash with concomitant viral disease & allopurinol Rx
Tetracycline	Diarrhea, N/V, drug-induced SLE, Tinnitus	
Antistaphylococcal PCN	Hypersensitivity, diarrhea, C diff, mp rash, AIN (methicillin)	
Antipseudomonal PCN (eg ceftazidime)	Hypersensitivity, diarrhea, C diff, mp rash, hyperNa	
Cephalosporins	GI upset, C diff, decreased platelet aggregation	PCN allergy
Aminoglycosides	Nephrotoxic, ototoxic, neuromuscular Blockade	Pregnancy, ESRD, myasthenia gravis DM, liver failure
Fluoroquinolones	GI upset, photosensitivity, confusion, dizziness, tendon rupture	Kids, pregnancy, seizure d/o (lowers threshold) Increases coumadin & theophylline
Nitrofurantoin	GI upset, peripheral neuropathy (ESRD and DM pts), pulmonary fibrosis, alopecia, hemolytic anemia in G6PD, pancreatitis, optic neuritis	ESRD, caution in G6PD deficiency, concomitant probenecid use, Mg use Quinolones are antagonistic
TMP/SMX	Hypersensitivity, rash, GI upset, Photosensitivity, Stevens-Johnson, Hematologic toxicity (AIDS pts)	Pregnancy Avoid in AIDS, elderly Increases coumadin
Vancomycin	Red-man syndrome (flushing, hypoTN, fever, chills, rash from histamine)	Avoid with other nephrotoxic and ototoxic drugs (bad in combo)

Which antibiotics are anti-Pseudomonal?

- ceftazidime (3rd generation)
- cipro
- aminoglycosides
- Pip-Tazo
- imipenem (carbapenem)

Which antibiotics have NO enterococcus coverage?

- cephalosporins
- septr
- cipro

Which antibiotic has poor Proteus & Pseudomonas coverage?

- nitrofurantoin

What are the factors important in determining choice of Abx for UTI?

- 1) complicated or uncomplicated UTI
- 2) spectrum of activity of Abx against probable pathogen
- 3) hx of hypersensitivity
- 4) potential side effects
- 5) cost

Which Abx DO NOT require renal dosing?

→ NO ADJUSTMENT EVER }}} “ KAMI Avoids Renal Dosing on C4”

- | | | |
|----------------|------------------|-------------------|
| - Ketoconazole | - Amphotericin B | - Clindamycin |
| - Azithromycin | - Rifampin | - Cloxacillin |
| - Moxifloxacin | - Doxycycline | - Ceftriaxone |
| - INH | | - Chloramphenicol |

→ only adjust if CrCl is <10

- Flagyl
- Erythromycin

Which Abx are CONTRAINDICATED in renal failure? }}} “Never Ever Take Sulfa Meds”

- Nitrofurantoin
- Ethambutol
- Tetracycline
- Sulfa drugs (long-acting)
- Methenamine

Which antibiotics should NOT be used with coumadin?

- Septra (probably worst)
- flagyl
- quinolones
- macrolides (erythromycin, azithromycin, etc)

List RFs for aminoglycoside toxicity.

→ drug factors

- high doses
- frequent doses (daily-dosing has lower toxicity)
- prolonged therapy (>3days)

→ patient factors

- older age
- pre-existing renal disease
- pre-existing hearing problems
- recent radio-contrast material
- coadministration of vancomycin, cyclosporine, amphotericin B

ANTIMICROBIAL PROPHYLAXIS

List host factors that increase the risk of infection (CHART)

- advanced age
- anatomic anomalies
- poor nutritional status
- smoking
- chronic steroid use
- immunodeficiency
- chronic indwelling hardware
- infected endogenous/exogenous material
- distant coexistent infection
- prolonged hospitalization
- sexual intercourse +/- spermicidals/diaphragm

List the recommendations for Abx prophylaxis for uncomplicated urologic procedures (CHART).

- catheterization (or removal) → single dose of cipro or septr DS for **only HIGH RISK pts**
- cystoscopy → single dose Ancef, cipro, Septra DS for **only HIGH RISK pts**
- UDS → single dose of cipro or septr DS for **only HIGH RISK pts**
- TRUS Bx → 1-4days of cipro for ALL
- TURP → amp + gent or cipro until Foley out for ALL
- TURBT → single dose of amp + gent or cipro for ALL
- SWL → single dose of Septra DS or cipro for ALL
→ if struvite, treat pre-op for UTI
- URS → single dose of amp + gent or cipro for ALL
- PNL/endopyelotomy → single dose of amp + gent or cipro for ALL
- Radical Nx → single dose of Ancef pre-op for ALL
- Sx w/ open GU tract (eg RP) → single dose of Ancef pre-op for ALL
- reconstruction w/ bowel → peri-op cefotetan/cefotixin or clinda + gent for ALL
- dirty wound → broad coverage or culture-directed Abx for **only HIGH RISK pts**

Outline the surgical wound classification (CHART)?

- clean } uninfected without inflammation or entry into genital, urinary, or GI tract
} primary wound closure closed drainage
- clean contaminated } uninfected with controlled entry into genital, urinary, or GI tract
} primary wound closure closed drainage
- contaminated } uninfected with major break in sterile technique (gross spillage)
- dirty infected } wound with pre-existing clinical infection or perforated viscera

What are the Abx recommendations for endocarditis prophylaxis?

- GU tract is 2nd most common site of entry of organisms that cause IE
 - ***Enterococcus faecalis* is most common organism**
- Abx for HIGH RISK and MODERATE RISK pts only
- HIGH RISK } ampicillin 2g + gentamicin 1.5mg/kg 30 minutes pre-op, then
ampicillin 25mg/kg or amoxicillin 25mg/kg 6hrs post-op
} vancomycin 1g iv (over 1-2hrs) + gentamicin 1.5mg/kg im 30min pre-op
- MODERATE RISK } amoxicillin 2g 1hr pre-op
} vancomycin 1g (over 1-2hrs) 30 minutes pre-op

*** AHA 2007 now recommends NO ROUTINE IE PROPHYLAXIS FOR GU PROCEDURES ***

*** if known UTI, then reasonable to pre-treat prior to procedure ***

*** if high-risk of active infection (prosthetic valve, previous IE, congenital heart dz, heart Tx with bad valve) it may be reasonable to give prophylaxis to cover enterococcus; ampicillin or amoxicillin ideal ***

What are the patients PREVIOUSLY identified to be at HIGH RISK of IE?

- high risk } prosthetic heart valves
 - } previous IE
 - } previous cyanotic congenital heart disease
 - } systemic-pulmonary shunts or conduits
- moderate risk } congenital heart malformations

What is the Abx recommendations for patients with orthopedic hardware (CHART)?

- **prophylaxis ONLY for patients with:**
 - total joints inserted <2yrs ago
 - hx of infected prosthesis
 - immunocompromised pts (steroids, DM, age, AIDS, etc)
 - urinary diversions
 - indwelling stents or catheters
 - recent hx of AUR or UTI
- cipro or ampicillin 2g + gentamicin 1.5mg/kg 30-60min prior
- vanco 1g (over 1-2hrs) if PEN allergic

BLADDER INFECTIONS

Uncomplicated cystitis

How common is uncomplicated cystitis?

- 10% of women per annum and 50% of women during their lifetime
- occasionally seen in young men, without underlying structural or fxn'al abnormalities
 - cystitis is considered COMPLICATED in men until proven otherwise

What is the presentation of cystitis?

- dysuria
- S/P pain
- frequency
- urgency
- hematuria
- foul-smelling urine
- NO fever, chills

List some of the RFs for development of UTIs (CHART)

- reduced urine flow
 - BOO (BPH, PCa, urethral stricture, stone)
 - neurogenic bladder
 - dehydration
 - urethral diverticulum
- colonization risk
 - sexual activity
 - spermicide use (increased bacterial binding)
 - estrogen-depletion eg menopause (increased bacterial binding)
 - Abx use (decreased natural flora)
- facilitation of ascent
 - catheterization
 - incontinence (urine or fecal)
 - residual urine with bladder wall ischemia

What are the etiologic organisms involved in uncomplicated cystitis?

- E. coli represents 75-90% in young women, S. saprophyticus represents 10-20%
- E. coli and other enterobacteriaceae most common in men

What are the bladder's defenses to development of UTIs? } } } "LOCAL Grown STUUF"

- | | |
|--|---|
| - Lactobacillus | - Salts (high) |
| - Organic acids (high) | - Tamm-Horsfall proteins (inhibits type 1 pili) |
| - Cytokines & PMNs | - Umbrella cell shedding |
| - Acidic urine pH | - Urea (high) |
| - Lactoferrin (scavenges essential Fe) | - Flow of urine (most important) |
| - Glucose (low) | |

What are the lab diagnostic findings of acute cystitis?

- U/A → pyuria, bacteriuria, hematuria
- urine C&S → $>10^2$ cfu/mL in symptomatic pts (NOT RECOMMENDED IN ALL PTS)

What is the DDX of dysuria?

- vaginitis
- urethral infections (gonorrhea, Chlamydia, herpes, trichomoniasis)
- noninflammatory urethritis
- CIS of bladder

What Abx are recommended for acute uncomplicated cystitis (CHART)?

- women } 3days of cipro, levo, Septra DS, Trimethoprim, Macrobid, norflox
- } 7days of Septra DS or cipro if DM, >65yrs, >1wk of symptoms, recent UTI, or use of diaphragm
- pregnancy } 7 days of amoxicillin, Keflex, nitrofurantoin, Septra (only in 2nd trimester)
- men } 7days of Septra DS or cipro

List PROS & CONS of using nitrofurantoin for UTIs.

→ PROS

- 1) minimal effect on fecal & vaginal flora
- 2) high urine concentrations
- 3) minimal bacterial resistance
- 4) cheap

→ CONS

- 1) no good tissue penetration for febrile UTIs (pyelonephritis)
- 2) ineffective against *Pseudomonas* & *Proteus*
- 3) QID dosing
- 4) no parenteral form

What is the f/u after initiation of Abx for cystitis?

- no f/u in women if asymptomatic after ABx
- f/u visit + U/A and C&S if high risk F or if M

What is the management of asymptomatic bacteriuria?

- 100% of patients with LT indwelling catheter, >50% of SCI pts on CIC, ~50% of elderly in NH (M&F), 1-5% of healthy pre-menopausal women
- not harmful in healthy adult pts
- screening ONLY recommended in **pregnant women & prior to urologic intervention**
- **Abx recommended ONLY for patients who are:**
 - 1) pregnant
 - 2) undergoing urologic procedures
 - 3) GU tract obstruction
 - 4) kids w/ VUR
 - 5) *Proteus* & *Pseudomonas* species

Complicated cystitis

What are the factors that suggest complicated UTI (CHART)? } } “ACADEMIC WHIP”

- AbN or anomalous GU tract } calyceal diverticulum, bladder diverticulum, neurogenic bladder, etc
- Children
- ABx use (recent)
- DM
- Elderly
- Male
- Immunosuppression
- Catheterized
- Week-long symptoms at presentation (7days)
- Hospital-acquired
- Instrumentation (recent)
- Pregnancy

What is the management of complicated UTIs (CHART)?

→ correct any underlying GU tract abnormalities

- if mild to moderate → 10-14days of cipro or Septra DS
→ commonly E. coli, Proteus, Klebsiella, or Pseudomonas
- if severe → iv amp + gent, cipro, ceftriaxone until afebrile
→ step-down to 14-21days of po cipro, Septra DS, levo (or culture-guided Rx)
→ post-Abx urine C&S

List causes of unresolved bacteriuria (CHART)

- 1) **bacterial resistance to ABx (most common)**
- 2) development of resistance from initially susceptible bacteria → occurs in 5%
- 3) bacteriuria caused by 2 bacterial species with mutually exclusive susceptibilities
- 4) rapid infection with a new, resistant species during original therapy
- 5) renal failure (urine concentration too low)
- 6) papillary necrosis from analgesic abuse
- 7) giant staghorn stone
- 8) self-inflicted infections or deception (variant of Munchausen's)

What is the management of unresolved bacteriuria?

- presume resistance
- 7days of different Abx
- adjust to C&S results

What factors increase morbidity associated with UTIs?

- obstruction
- urease splitting bacteria (“PACK PUSSY”)
- DM (especially with emphysematous pyelo)
- SCI with high bladder pressures
- catheter drainage
- pregnancy
- acute prostatitis
- renal papillary necrosis

- foley drainage
- broad spectrum Abx
- control of DM (glucosuria)
- +/- anti-fungals if yeast cultured

List urologic complications of DM (AUA Update #26 – 2004) } } } “Bladder VENUE”

- 1) Bladder cystopathy
 - classically see increased capacity + decreased sensation + possible atony
 - get increased bladder wall hypertrophy, but less effective contractions
- 2) renal Vascular disease (atherosclerotic) } lead to HTN and ischemic nephropathy
- 3) ED } prevalent in 50% with type 1 DM, 45% with type 2 DM
 - **related to abN levels of eNOS/nNOS activity, NO, complementary GMP & protein kinases**
- 4) Nephropathy } most common cause of ESRD in N. American & European adults
 - **mediated by advanced glycosylation end products (AGEs)**
 - microalbuminuria & HTN present at stage 3 DM nephropathy
- 5) UTI } 2 to 10-fold higher risk, especially diabetic women
 - due to **hyperglycemia** and subsequent defects in cellular immunity
- 6) Emphysematous cystitis/pyelonephritis } *E. coli* & *Klebsiella* are most common pathogens
 - **requires gas-forming bacteria, ↑'d tissue glucose level, impaired tissue perfusion**

What is the central pattern of histopathological change seen in DM kidneys. (AUA Update #26 - 2004)

- **augmentation of extracellular material within glomerular compartment**
- involves AGEs, fibronectin, $\alpha 2$ type 4 collagen, laminin A/B1/B2, heparin sulfate, sorbitol, PK-C

KIDNEY INFECTIONS

How do renal infections present?

- extremely variable } from cystitis + mild flank pain to gram-negative sepsis
- fever, chills, flank pain + irritative symptoms } may not be present, esp in DM, elderly, SCI
- may have GI symptoms of N/V, abdo pain, diarrhea } may be asymptomatic
- bacteriuria and pyuria with large amounts of WBC casts
- urine culture may be negative if ureter is obstructed or if infection is not in collecting system
 - **~20% can have negative urine C&S**
- +ve blood culture in ~25% and usually replicates urine C&S results
- may not have renal impairment (variable)

Acute pyelonephritis

What are the pathologic findings of pyelonephritis?

- hematologic dissemination } multiple focal areas of suppuration on surface of kidney
 - } focal destruction of glomeruli and tubules
 - } rest of cortex and medulla are NOT involved
- ascending infection } linear bands of inflammation from medulla to renal capsule
 - } focal wedge-shaped area of acute interstitial inflammation
 - } PMN leukocytes or plasma cells +/- bacteria
- chronic pyelo } cortical scar associated with retraction of corresponding renal papilla
 - } patchy involvement with numerous chronic inflammatory foci
 - } normal glomeruli outside scarred areas
 - } papillary deformity, sclerosis and sometimes necrosis

What are the common organisms associated with acute pyelonephritis?

- **E coli represents ~80%**
- *Klebsiella*
- *Enterobacter*
- *E. faecalis*
- *Proteus*
- *Pseudomonas*
- *S.epidermidis/S.aureus*

What are the radiologic findings suggestive of acute pyelonephritis?

→ **most cases have N imaging (eg 75% of IVPs are N)**

- 1) IVP → renal enlargement (>15cm or >1.5cm compared to other side) } **most common abN finding on IVP**
 - diminished nephrogram phase
 - delayed urogram phase
 - compressed collecting system (eg spidery calyces)
 - ureteral dilatation (endotoxin-mediated impairment of peristalsis)
- 2) ultrasound → renal enlargement } **most common abN finding on U/S (usually N)**
 - hypoechoic parenchyma
 - compressed collecting system
 - may see abscess
- 3) CT → renal enlargement
 - streaky hypoattenuation of renal parenchyma } **most common CT finding**
 - perinephric stranding (or even perinephric abscess)
 - cortical striations
 - may see compressed or dilated collecting system (hydronephrosis)
 - urothelial thickening
 - paraureteral or parapelvic lucency

What is the management of acute pyelonephritis?

→ **ACUTE PYELONEPHRITIS DOES NOT CAUSE SCARRING IN NORMAL GU TRACT**

- 1) uncomplicated (no sepsis, no N/V) → urine culture
 - +/- imaging (U/S or CT to r/o stones or obstruction)
 - outpt Abx for 10days (cipro / Septra DS)
 - if NO improvement, admit, review cultures, start iv Abx, r/o obstruction or abscess
 - if improvement, culture after ABx's + prn urologic evaluation
- 2) complicated or sepsis → blood & urine cultures
 - imaging
 - iv Abx (cipro / amp + gent / ceftriaxone) x 3days } 7 days if +ve blood C&S
 - if NO improvement, r/o abscess or persistent obstruction, re-culture
 - once afebrile, po Abx for 10-14 days (cipro / Septra DS / Keflex)
 - culture after Abx therapy (at 2weeks then again at 4-6 weeks)

Acute Focal or Multifocal Bacterial Nephritis (Lobar nephronia)

How does acute focal or multifocal bacterial nephritis differ from acute pyelonephritis?

- uncommon, severe form of acute renal infection
- infection confined to single renal lobe or multiple lobes
- more severe than acute pyelo → 50% are DM, 50% are bacteremic, sepsis common
- **likely an early phase of frank renal abscess**

What are the CT findings suggestive of acute bacterial nephritis (lobar nephronia)?

- non-enhancing area
- wedge-shaped lesion in kidney
- poorly marginated
- mass effect within kidney (can resemble tumour)

What is the management of acute bacterial nephritis?

- hydration
- iv Abx for x ≥ 7days, then po Abx for 7days } if no improvement, need to r/o obstruction, abscess, RCC
- **usually responds to medical therapy**

Emphysematous pyelonephritis

What is emphysematous pyelonephritis?

- **acute necrotizing parenchymal & perirenal infection caused by gas-forming organisms**
- usually occurs in DM
 - obstruction with stones or papillary necrosis common only in NON-DM's
- **E. coli a common pathogen** } Klebsiella also seen often
- considered a complication of severe pyelonephritis } **overall mortality ~20-40%**
- **all in adults, women more commonly (6x)**
- most have triad of fever, N/V, and flank pain

What are the radiologic findings of emphysematous pyelonephritis?

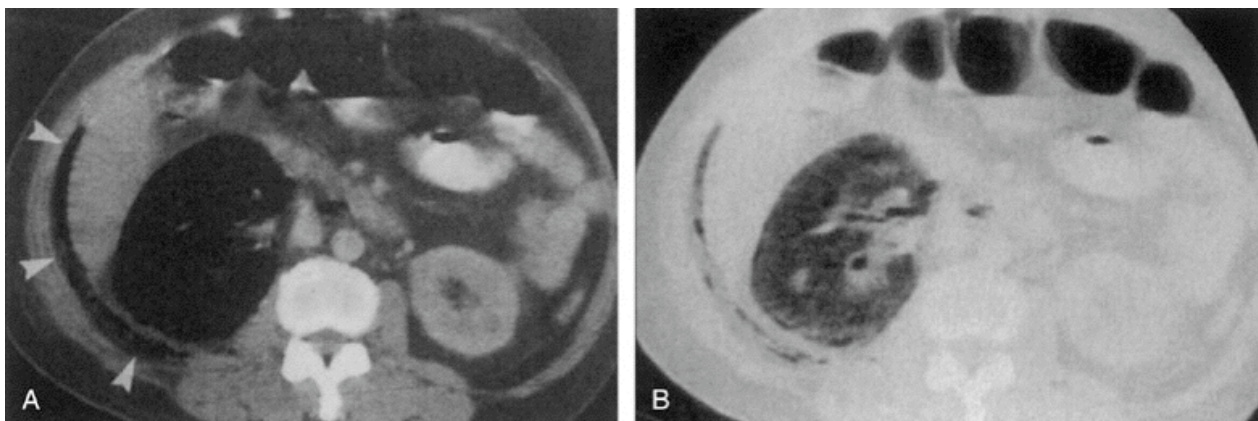
- obstruction seen in ~25%
- U/S shows strong focal echoes suggesting intraparenchymal gas
- CT is imaging modality of choice
- Type I } 50% mortality rate
 - **no fluid** in renal or perirenal tissue
 - **streaky or mottled gas** in or around kidney +/- gas in collecting system
- Type II } 20% mortality rate
 - + renal or perirenal **fluid**
 - no streaky or mottled gas in kidney
 - + **bubbly or loculated gas in collecting system**

What is the management of emphysematous pyelonephritis?

- **can be a surgical emergency** } **most pts are septic**
- hydration
- broad-spectrum iv Abx
- relief of obstruction if present } drainage
- Nx if type I or no signs of improvement after a few days of therapy

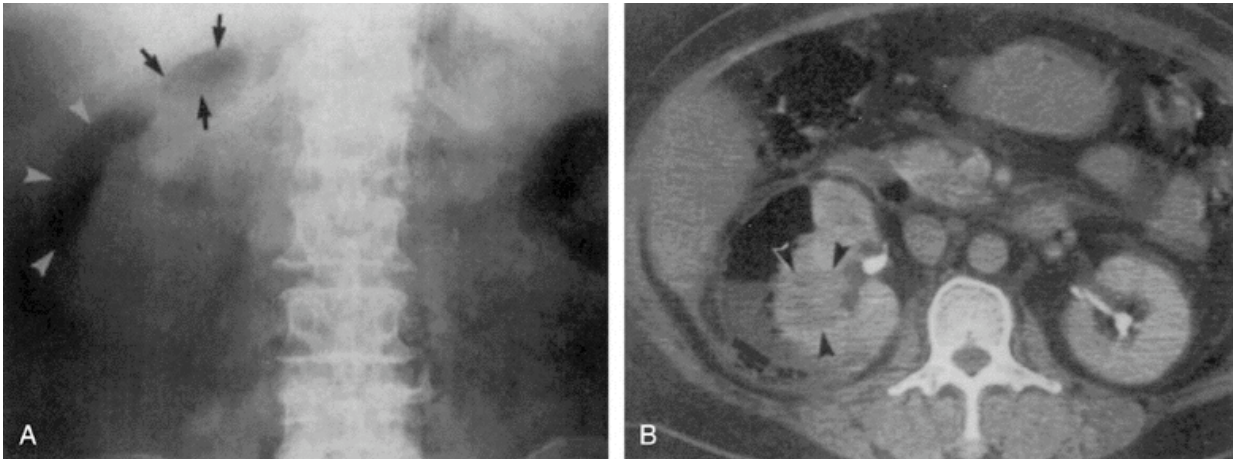
What are the indications for immediate Nx in emphysematous pyelonephritis?

- 1) type 1
 - 2) no improvement with conservative therapy
 - 3) critically ill + ARF/shock/thrombocytopenia/mental status changes
- unless bilateral } trial of drainage + iv Abx



→ **TYPE I EMPHYSEMATOUS PYELONEPHRITIS**

- no renal or perirenal fluid
- mottled, streaky gas appearance in or around kidney
- +/- bubbly or loculated gas in collecting system
- complete destruction of kidney



→ TYPE II EMPHYSEMPTATOUS PYELONEPHRITIS

- ++ renal or perirenal fluid
- bubbly or loculated gas in collecting system

Renal Abscesses

What are renal abscesses?

- collection of purulent material confined to renal parenchyma
- **usually due to gram –ve bacteria** → used to be gram +ve (days before Abx)
→ usually from ascending infection associated with tubular obstruction from prior infections or stones
- 2/3 of gram –ve abscesses are associated with stones or damaged kidneys
- gram +ve abscesses are usually from bloodborne sources

How do renal abscesses present?

- may present with fever, chills, abdo pain or flank pain (may have wt loss and malaise)
- may have a hx of a recent gram +ve infection (1-8weeks) before GU tract symptoms
- marked elevation in WBC
- pyuria and bacteriuria usually absent if gram +ve (bloodborne) abscess
- +ve blood cultures

What conditions predispose a patient to renal abscesses?

- iv drug use
- skin carbuncles
- recurrent lung infections
- complicated UTIs associated with:
 - stasis
 - stones
 - DM
 - pregnancy
 - neurogenic bladder

What are the IVP findings suggestive of an acute renal abscess?

- hard to differentiate early renal abscess from acute pyelonephritis
- generalized renal enlargement
- distortion of renal contour
- renal fixation with respiration
- obliteration of corresponding psoas shadow
- delayed or absent nephrogram if diffuse renal involvement

What are the IVP findings suggestive of a chronic renal abscess?

- renal mass lesion
- poorly defined or distorted calyceal system
- radiolucency in affected area on nephrotomogram

What are the U/S findings suggestive of a renal abscess?

- hypoechoic or echo-free space-occupying lesion with increased transmission
- poorly marginated
- strong internal echo with shadow if air

What are the CT findings suggestive of a renal abscess?

- diagnostic procedure of choice
- well defined pre and post-contrast
- early } renal enlargement with focal, rounded areas of hypoattenuation
- later } ring-enhancing thickened-wall with hypoattenuating parenchymal mass
 - } obliteration of adjacent tissue planes and thickening of Gerota's fascia

What is the management of a renal abscess?

- FNA if suspicious of a hypervascular tumour
- general therapies:
 - iv Abx
 - hydration
 - serial reimaging
- perc drainage if:
 - <3cm in immunocompromised pt
 - >3cm (consider open drainage if >5cm)
 - no response to Abx
- if hematogenous origin suspected → cephalosporin or vancomycin
- if gram -ve suspected → 3rd generation cephalosporin, ampicillin, gentamicin

Pyonephrosis

What is pyonephrosis?

- **infected hydronephrosis associated with suppurative destruction of renal parenchyma**
- concomitant total or nearly total loss of renal function
- early Dx and treatment are essential to avoid sepsis and permanent loss of renal function

What is the presentation of pyonephrosis?

- **very ill patient with high fever, chills, flank pain and tenderness**
- may occasionally present with fever and vague GI symptoms
- may not have bacteriuria if ureter is completely obstructed
- common to have hx of stone, UTI, or GU tract surgery

What are the radiologic findings suggestive of pyonephrosis?

- U/S } internal echoes within dependent portion of dilated pyelocalyceal system
 - } focal areas of decreased echogenicity within hydronephrotic parenchyma
- CT } nonspecific
 - } poorly functioning kidney with thinned parenchyma
 - } pelvicaliectasis
 - } may show thickening of renal pelvis, perinephric stranding, and striated nephrogram

What is the management of pyonephrosis?

- iv Abx
- drainage of infected renal pelvis
- once stable, find source of obstruction

Perinephric abscesses

What are PERI-nephric abscesses?

- due to either a) rupture of an acute renal abscess or b) from hematogenous seeding
- **DM present in ~1/3 of cases**
- perinephric abscesses formation susceptible in pts with pyonephrosis or perinephric hematoma
- PCKD on HD are also susceptible to perinephric abscesses

What are the causes of perinephric abscesses?

- bowel perforation
- Crohn's disease
- spread of osteomyelitis from thoracolumbar spine
- usually E coli, Proteus, and S aureus

What are PARA-nephric abscesses?

- perinephric infection that has ruptured through Gerota's fascia or from other local sources
- may be from infectious disorders of the bowel, pancreas, or pleural cavity

How do perinephric abscesses present?

- often insidious onset
- similar presentation to pyelonephritis but often afebrile } 30% afebrile
- abdo or flank mass palpable in ~50%
- psoas abscess may present with a limp and flexion and external rotation of ipsilateral hip
- elevated WBC, elevated creatinine, pyuria found in 75%

What are the radiologic findings suggestive of a perinephric abscess?

- IVP } abnormal in 80% of cases, but nonspecific abnormalities
 - } absence of psoas shadow, mass in perirenal area with blurred renal outline, and elevated or immobile diaphragm
 - } may see extraluminal gas surrounding kidney if gas-forming organism
- ultrasound } variable
 - } ranges from anechoic mass displacing kidney to echogenic collection that blends with normally echogenic fat within Gerota's fascia
- CT } primary modality of choice
 - } shows primary abscess and route of spread of infection

What is the management of perinephric abscesses?

- Abx based on urine & blood cultures may often be inadequate } predicts abscess organism only ~50% of the time
- **usually doesn't respond to Abx alone** } suspect abscess if still febrile after 4-5days of Rx
- **perc drainage of small collections**
- open surgical drainage (or Nx if nonfunctioning or severely infected) for larger collections
- treatment of underlying problem
- delay in Dx is often the main reason for high morbidity associated w/ perinephric abscesses
 - if symptomatic for >5days or febrile despite Abx for >4days, think abscess

Chronic Pyelonephritis

How common is chronic pyelonephritis?

- **rare in patients without underlying renal or GU tract disease**
- causes ESRD almost exclusively in patients with underlying renal or GU tract disease
- usually associated with recurrent UTIs, VUR, analgesic abuse, stones, or obstruction
- NOT associated with HTN

How does chronic pyelonephritis present?

- **usually asymptomatic until in renal failure**
- if due to recurrent episodes of acute pyelo then may have hx of intermittent symptoms of fever, flank pain, dysuria
- bacteriuria and pyuria are not predictive of renal infection
 - urine may be sterile if ureter is obstructed or infection is outside of collecting system

What are the IVP features of chronic pyelonephritis?

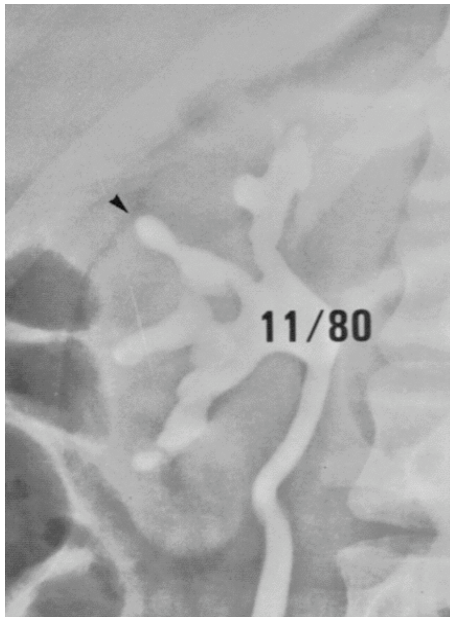
- involved kidneys are usually small & atrophic
- asymmetry & irregularity of the kidney outlines
- **blunting & dilation of ≥1 calyces**
- **cortical scars overlying the blunted/dilated calyx**
- compensatory hypertrophy in contralateral kidney

What is the DDx of a dilated calyx with scarring of overlying cortex?

- chronic pyelo
- analgesic nephritis with papillary necrosis
- stones/obstruction of calyx
- renal infarction
- TB

What is the management of chronic pyelonephritis?

- goals of treatment are:
 - } treating infection, if present
 - } preventing future infections
 - } monitoring and preserving renal function
- Abx should be C&S driven, prolonged, and not nephrotoxic
- in N urinary tracts, recurrent UTIs are NOT caused by relapse from bacterial persistence in renal parenchyma



→ CHRONIC PYELO } irregular renal outline with scarred parenchymal overlying dilated calyx

Xanthogranulomatous Pyelonephritis (XGP)

What is XGP?

- the great imitator
- **a rare, severe, chronic renal infection typically resulting in diffuse renal destruction**
- usually **unilateral** and results in **non-functioning, enlarged kidney** associated with **obstructive uropathy secondary to stones**
- characterized by accumulation of **lipid-laden foamy macrophages (xanthoma cells)**
- starts within pelvis and calyces and extends into and destroys parenchyma and adjacent tissues
- can resemble RCC
- bacteria are usually of low virulence } bacteremia rare

What are the causes of XGP?

- **primarily involves stones + obstruction + infection**
- may also involve:
 - venous occlusion and hemorrhage
 - lymphatic blockage
 - altered immunologic competence
 - abnormal lipid metabolism
 - failure of Abx therapy for UTI
 - renal ischemia

What does a XGP kidney look like on pathology?

- massively enlarged with normal contour } diffuse in ~80% but can be segmental
- usually has stones and peripelvic fibrosis } peripelvic fibrosis prevents pelviectasis
- dilated calyces that are filled with purulent material
- papillary necrosis
- in advanced disease, multiple abscesses seen in thinned parenchyma

How does XGP usually present?

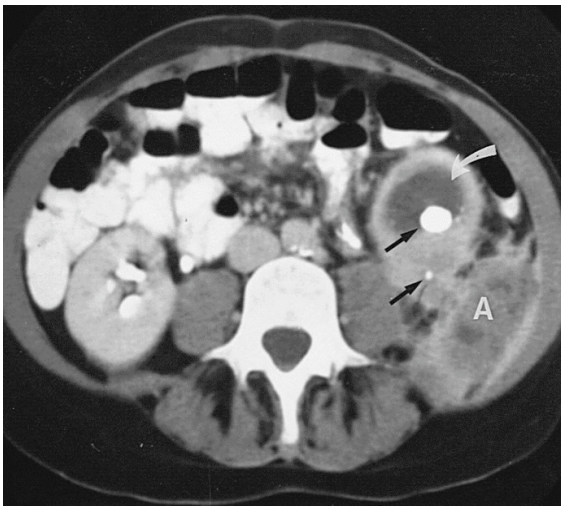
- **classic triad**
 - **unilateral enlargement**
 - **non-functioning or poorly functioning kidney**
 - **large stone in renal pelvis**
- may resemble mass indistinguishable from malignant tumour
- 70% have flank pain, fever, and chills
- 50% have persistent bacteriuria
- 60% have flank mass
- 35% have hx of stones
- **malaise, anorexia, wt loss, Hx of UTIs**
- may rarely present with HTN, hematuria, and hepatomegaly
- more common in **women and DM**
- **usually unilateral** } so renal failure uncommon
- usually presents in 40's to 60s
- usually have pyuria and proteinuria on U/A
- often anemic with evidence of hepatic dysfunction
- **Proteus is most common organism** (E coli also very common)

What is the DDx of XGP?

- pyonephrosis } usually doesn't have stones
- renal malacoplakia } usually don't have stones
- renal lymphoma } usually bilateral and not associated with stones
- RCC } can resemble clear cell RCC on frozen section

What are the radiologic findings suggestive of XGP?

- unilateral enlargement
- renal pelvic stone
- poorly functioning or nonfunctioning kidney
- may resemble mass
- contrast CT may show ulcerated pyelocalyceal system with multiple irregular filling defects
- CT is ideal imaging modality
 - large reniform mass w/ renal pelvis tightly surrounding a central calcification but without pelvic dilatation
 - renal parenchyma is replaced by multiple water-density masses (dilated calyces & abscesses) filled with debris and pus
 - enhancement of wall of abscess cavities but cavity itself doesn't enhance
- U/S
 - global enlargement of kidney
 - normal renal tissue replaced by multiple hypoechoic fluid-filled masses
 - stone in collecting system
- renal scan
 - DMSA used to quantify differential lack of function



→ CT SCAN OF XGP } stones (black arrows) with LP pyonephrosis (curved arrow) + perinephric abscess (A)

What is the management of XGP?

- often wrongly diagnosed
- Abx } usually peri-op ... but occasionally, long-term ABx may eradicate infection & restore renal fxn
- partial Nx for localized XGP
- Nx for diffuse XGP } open approach recommended
- Radical Nx if RCC suspected } has been associated with RCC, papillary TCC of renal pelvis or bladder, infiltrating SCC of pelvis

Malacoplakia

What is malacoplakia?

- **inflammatory disease** that can affect entire GU tract, GI tract, skin, lungs, bones, & mesenteric LNs
 - can occur in almost any organ **BUT 75% are GU (bladder most common, then kidney)**
- soft, yellow-brown plaques with granulomatous lesions with **Michaelis-Gutmann bodies**
- **probably results from abN macrophage function in response to bacteria** } usually E coli
 - imbalance of cGMP/cAMP } cGMP too low & cAMP too high
- **Dx made on Bx**

What are Michaelis-Gutmann bodies?

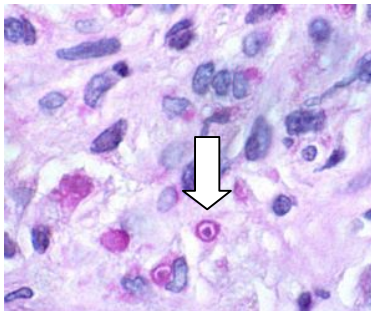
- incompletely destroyed bacteria surrounded by lipoprotein membrane
- **laminated lysosomal inclusion bodies** } laminated in Ca PO₄ crystals

What is the cause of malacoplakia?

- **unknown** } ?**coliform bacteria** in immunocompromised pts (AIDS, autoimmune disease, Ca, etc)
- likely involves defect in bacterial digestion with unusual immunologic response

What does malacoplakia look like on pathology?

- 1) large **histiocytes (von Hanselmann cells)**
- 2) small **basophilic granules (Michaelis-Gutmann bodies)** → pathognomonic but NOT essential for Dx
→ **contain large amounts of immunoreactive α1-antitrypsin**



How does malacoplakia present?

- most patients are >50yrs old
- **4x more common in F** } only seen in GU tract malacoplakia
- **usually immunosuppressed or debilitated** } **persistent coliform UTIs in ~90% (E. coli)**
- bladder → irritative symptoms with hematuria & smooth filling defects in bladder
- renal malacoplakia → associated with renal vein thrombosis & IVC thrombosis
- testicular malacoplakia → associated with epididymo-orchitis
- mortality can be >50%

What are the radiologic findings suggestive of renal malacoplakia?

- multifocal malacoplakia usually presents as enlarged kidneys with multiple filling defects
→ NO renal calcifications, stones, or hydro
→ on CT, malacoplakia lesions are **less dense than surrounding renal parenchyma**
- unifocal malacoplakia usually appears as a noncalcified mass that is indistinguishable from other inflammatory or neoplastic lesions
→ on CT, may see solid or cystic structure, depending on degree of internal necrosis

What is the DDx of renal malacoplakia?

- renal cystic disease (can tell with good CT)
- renal inflammatory disease
- RCC (not usually multifocal)
- XGP (usually have stones and UTI symptoms)

What is the management of renal malacoplakia?

- **goal is to control the UTIs → should stabilize the disease process**
- Septra DS, rifampin, doxycycline, and cipro recommended because of intracellular bactericidal activity
→ cipro good because taken up by macrophages
→ add **ascorbic acid & bethanechol** to ↑ normal macrophage function (especially if NO UTIs)
- bladder malacoplakia Rx'd initially by TUR + ABx } renal malacoplakia usually Rx'd surgically
- **Nx recommended if in Tx kidney, multi-focal distribution or refractory to ABx**
→ death w/in 6mos if B/L renal malacoplakia or in Tx kidney
- LT-survival after nephrectomy good for unilateral renal disease

Renal Echinococcosis

What is renal echinococcosis?

- **parasitic infection caused by larval stage of tapeworm Echinococcus granulosus**
 - in adult form, it resides in intestines of the dog (definitive host)
 - ova of adult worm in feces of the dog are ingested
 - larvae hatch and penetrate venules of duodenum and travel to liver, then lungs
 - larvae that make it through liver and lungs can then infect kidneys
 - larvae undergo vesiculation and the resultant hydatid cyst grows at 1cm/yr
- seen in dogs, sheep, cattle
- seen in humans in S. Africa, Australia, New Zealand, Mediterranean countries (esp Greece), Eastern Europe, American Indians
- **echinococcosal cysts of the kidney are usually single and located in the cortex**
- **cyst contents are highly antigenic** } risk of fatal anaphylaxis

What does renal echinococcosis look like on pathology?

- hydatid cyst has 3 zones;
 - peripheral zone } fibroblasts that may calcify
 - intermediate layer } laminated layer that becomes hyalinized
 - inner layer } nucleated epithelium known as the germinal layer
 - } new larvae develop in this germinal layer within brood capsules
 - } detached brood capsules are called daughter cysts
 - } hydatid sand is free larvae + daughter cysts

How does renal echinococcosis present?

- **most are asymptomatic**
- **often presents like slow growing tumour** } **flank mass, dull pain, and hematuria**
- cyst is focal and so DOES NOT cause renal failure
- if cyst ruptures into collecting system, pt may have renal colic from passage of debris
 - hydatiduria (resembles grape skins)
- if cyst ruptures will also seen daughter cysts in urine; may see laminated wall of cyst
- may see eosinophilia

How do you Dx renal echinococcosis?

- **daughter cells in urine**
- laminated wall of cyst in urine
- +ve double-diffusion test using partially purified hydatid arc 5 antigens
- complement fixation, HA, and Casoni intradermal skin tests are less reliable

What are the radiologic findings suggestive of renal echinococcosis?

- IVP } thick-walled cystic mass, occasionally calcified
 - } if cyst ruptures may see daughter cysts outlined in renal pelvis
- ultrasound } multicystic or multiloculated mass
 - } movement shows bright falling echoes within (hydatid sand)
- CT } **cystic mass w/ discrete, round daughter cysts & well-defined enhancing membrane**
 - } may also present as thick-walled multiloculated cystic mass (less specific)

What is the DDX of renal echinococcosis?

- simple cyst
- renal abscesses
- infected cysts
- necrotic RCC
- presence of daughter cysts within mother cyst differentiates renal echinococcosis

What is the management of renal echinococcosis?

→ **DO NOT FNA } ruptures cyst and releases highly antigenic contents (anaphylactoid rxn)**

→ prognosis is good but depends on site and size of cysts

1) medical therapy } mebendazole → limited success with significant S/Es

2) **surgery } mainstay of treatment**

} removal of cyst without rupture (reduce chance of seeding and recurrence)

} if wall is calcified, larvae are dead so low risk of seeding

- be careful of living daughter cells

} if cyst must be ruptured, aspirate first then instill into cyst some 2% formalin or 1% iodine

BACTEREMIA, SEPSIS, AND SEPTIC SHOCK

What is sepsis?

- clinical syndrome, in response to an infection, characterized by extremes of:

→ temperature → RR

→ HR → WBC count

- occurs when a local infectious process becomes an uncontrolled systemic blood-borne inflammatory response resulting in damage to tissues/organs remote from initial infection

What is bacteremia?

- presence of viable bacteria in blood

What is systemic inflammatory response syndrome (SIRS)?

- clinical syndrome characterized by extremes of temperature, HR, RR, immune response

- can occur in response to systemic infection, trauma, thermal injury, or sterile inflammation

How is sepsis defined (CHART)?

- SIRS + infection

→ general

- fever >38.3 or hypothermia <36

- HR >90

- tachypnea

- altered mental status

- significant edema or +ve fluid balance

- hyperglycemia in the absence of DM (>7.7 mol/L)

→ inflammatory

- WBC >12 or <4

- normal WBC count with $>10\%$ immature forms

→ organ dysfunction

- arterial hypoxemia ($\text{PaO}_2/\text{FiO}_2 >300$)

- acute oliguria

- creatinine increase of 0.5mg/dL

- coagulation abnormalities (INR 1.5 or PTT $>60\text{sec}$)

- ileus

- platelets <100

- elevated bilirubin (>70 mmol/L)

→ tissue perfusion

- lactate >1

- decreased cap refill or mottling

What is septic shock?

- extreme form of sepsis complicated by organ dysfunction and hemodynamic instability despite fluids and pharmacologic resuscitation

What is the pathophysiology of sepsis?

- **bacteria (namely, the cell wall component) are primarily responsible for septic shock**
 - they activate macrophages, neutrophils, dendritic cells, and complement system
- prime initiator of gram –ve sepsis is **endotoxin** (LPS component of bacterial outer membrane)
 - endotoxin induces activation of cytokines } leads to vasodilation & endothelial leak
 - overactivation of cytokines like TNF, IL-1, IL-4, IL-10
- monocytic cells play key role in mediating biologic effects of SIRS and septic shock
 - monocytes remove and detoxify LPS endotoxin
 - endotoxin-activated monocytes can also produce cytokine though

How do septic patients present?

- fever >38C or hypothermia <36C
- tachycardia >90
- tachypnea → may get respiratory alkalosis
- altered mental status
- WBC count >12 or <4
- elevated bilirubin, lactate, BS, C reactive protein
- coagulation abnormalities
- evidence of organ dysfunction } oliguria, hypoTN, ileus

What are the causative organisms in sepsis?

- 30-80% are gram –ve bacteria } E coli is most common
 - } nosocomial organisms include Pseudomonas, Proteus, Serratia
- 5-25% are gram +ve bacteria } increasing cause of sepsis
- fungal sepsis } also increasing

What is the management of sepsis?

- **goal directed therapy**
- resuscitation & optimization of perfusion
- supportive care → evidence supports benefit of using activated protein C, an inhibitor of inflammatory and coagulation pathways
- monitoring
- broad-spectrum Abx } aminoglycoside is Abx of choice if GU source suspected
- elimination of infectious source
- involve critical care team

What are the 3 clinical factors that are predictive of finding a resistant pathogen?

- 1) recent use of Abx in last month
- 2) advanced age
- 3) male sex

BACTERIURIA IN PREGNANCY

How common is bacteriuria during pregnancy?

- **prevalence same as in non-pregnant women**
- **asymptomatic bacteriuria is most common infectious complication of pregnancy**
- asymptomatic bacteriuria DOES NOT CLEAR spontaneously as frequently as in nonpregnant women
 - more symptomatic and tend to remain bacteriuric
- site of infection doesn't change with pregnancy
- more common later in pregnancy, in low SES, multiparous women, and women with sickle cell trait
- women w/ renal source of bacteriuria are more likely to have persistent postpartum bacteriuria

How common is pyelonephritis during pregnancy?

- **develops in 1-4% of all pregnant women** } 20-40% of pregnant women w/ unRx'd bacteriuria
→ **~75% get pyelo during T3** } when hydro and stasis in GU tract is greatest
- 1/3 of pregnant women that get pyelo have a prior hx of pyelo
- screening for bacteriuria decreases incidence of acute pyelo
- those with infections localized to kidney have increased evidence to suggest hx of chronic pyelo
→ increased likelihood that bacteriuria progresses to acute pyelonephritis during pregnancy

What are the complications associated with bacteriuria during pregnancy?

- higher incidence of pyelo & sepsis } **↑'d incidence of prematurity, low birth wt & fetal death**
- ?slightly higher risk of developing anemia

What are some of the physiologic changes of pregnancy? } AUA Update - 2005

- 1) hematologic
 - 50% increase in plasma volume, 15% increase in RBC volume } decreased Hct
 - 25-40% increase in total blood volume
 - leukocytosis
 - hypercoagulable state } increased factors 7, 8, 10, fibrinogen
} decreased fibrinolysis
→ highest risk of DVT during T3 & immediately post-partum
(NB – heparin does NOT cross placenta)
- 2) cardiovascular
 - 30-50% increase in CO by T3
 - ↓'d SVR } progesterone effect
 - ↓'d venous return with large gravid uterus compressing IVC
- 3) respiratory
 - 20% reduction in FRC
 - 15% increase in O₂ consumption
 - ↑'d risk of rapid decline in PaO₂
- 4) GI
 - GERD and slower gastric emptying } progesterone
} gastrin secretion (placenta) lowers gastric pH
→ increased risk of peri-op aspiration
- 5) GU
 - Renal
 - 1) ↑'d renal size } renal length increases approximately 1 cm
 - 2) ↑'d RBF
 - 3) ↑'d GFR: 30-50%
 - 4) ↑'d protein excretion (normal up to 300mg/day)
 - 5) ↑'d urine Ca, citrate, and uric acid excretion
 - 6) ↓'d Cr and BUN
 - 7) ↑'d susceptibility to pyelonephritis
 - 8) urine volume increases in upper tract
 - Collecting system
 - 9) hydronephrosis
 - more common on R } left side protected from compression by sigmoid
 - decreased peristalsis during pregnancy
 - most women in 3rd trimester show significant ureteral dilatation (90% in T3)
→ initially due to muscle-relaxing effects of increased progesterone
→ **later due to mechanical compression by enlarging uterus**
 - Bladder & Urethra
 - 10) bladder becomes hyperemic
 - 11) bladder hypertrophy
 - 12) squamous changes of the urethra } due to estrogen
 - 13) SUI
 - 14) storage LUTs

What are the recommendations for screening for bacteriuria?

- **urinalysis + urine C&S during T1** } if negative, no need to test further as these patients are unlikely to develop bacteriuria later
- u/a alone has too high a false -ve rate
- if hx of recurrent UTIs or VUR, may benefit from Abx prophylaxis

What is the management of bacteriuria during pregnancy?

- pathogens similar to those seen in non-pregnant women
- must consider fetal toxicity
- **full 3-7 day course recommended**
- **f/u cultures recommended**
- if bacterial persistence or rapid reinfection consider Abx prophylaxis during pregnancy
- if acute pyelonephritis mother should be admitted and receive iv Abx
→ 14days po Abx once afebrile then low-dose prophylactic Abx

Which Abx are safe during pregnancy?

- penicillins are SAFE } eg ampicillin 500 qid, amoxicillin 250 tid
- cephalosporins are SAFE } eg keflex 500 qid
- nitrofurantoin SAFE EXCEPT IN T3 and if no hx of G6PD def. } eg 100mg qid
- sulfonamides SAFE ONLY in T2 and if no hx of G6PD def. } eg DS bid
} may cause kernicterus

Which antibiotics should be avoided during pregnancy?

- fluoroquinolones (cartilage damage in beagle pups)
- tetracyclines (discoloured teeth, bone abN'ities)
- chloramphenicol (grey baby syndrome → hypoTN, hypothermia, CV collapse)
- sulfonamides } not safe in T1 (NTDs) or T3 (kernicterus, hemolytic anemia)
- aminoglycosides (deafness)
- trimethoprim } not safe in T1 (structural defects – folic acid) or maybe T3 (megaloblastic anemia)
- nitrofurantoin } not safe in T3 (hemolytic anemia)
- ??? erythromycin (maternal cholestatic jaundice) \ recent data suggest
- ??? flagyl (teratogenic) / they are safe

BACTERIURIA IN THE ELDERLY

How common is bacteriuria in the elderly?

- 20% of women and 10% of men older than 65yrs have bacteriuria
- ratio tilted towards men with increased age → only 2:1 in favour of women
- most are asymptomatic

What are some RFs for developing bacteriuria in the elderly?

- indwelling catheter/condom catheter
- hydronephrosis
- stones
- DM
- congenital urologic disease
- BOO
- female with cystocele
- living in an institution

Why are the elderly at increased risk of developing bacteriuria?

- decline in cell-mediated immunity
- neurogenic bladder dysfunction
- increased perineal soiling (hygiene) from urinary and fecal incontinence
- increased incidence of urethral catheterization
- estrogen-related changes in vaginal environment

What are the causative pathogens of bacteriuria in the elderly?

- different from pathogens seen in younger patients
- **E coli still most common } 75%**
- increased incidence of Proteus, Klebsiella, Enterobacter, Serratia, and Pseudomonas
- gram +ve bacteriuria more common in elderly M than F
- polymicrobial bacteriuria more common in elderly
- increased resistance in the elderly

How does bacteriuria present in the elderly?

- **usually asymptomatic**
- even severe upper tract infections may not be associated with fever and leukocytosis
- pyuria is sensitive but not specific in elderly } 60% with pyuria don't have bacteriuria
- sepsis is more common in the elderly
- **screening for asymptomatic bacteriuria NOT RECOMMENDED in elderly**
(only recommended in pregnancy and prior to urologic procedure)
- 10-15% higher resistance to Septra, cipro, penicillins, cephalosporins in NH residents

What is the management of bacteriuria in the elderly?

- **treatment of asymptomatic bacteriuria NOT RECOMMENDED, even in NH patients**
- bacteriuria leading to UTI in elderly pts with abnormal GU tract (eg BOO) or systemic diseases (eg DM) can lead to renal failure and need prompt Abx
- UTIs caused by urea-splitting bacteria (eg Proteus, Klebsiella) can lead to struvite stones and renal failure so need prompt Abx
- 7days of Abx recommended, 14 days if febrile or systemic infection
 - goal is to eliminate symptoms but not necessarily to sterilize urine
- elderly more susceptible to toxic and adverse effects of Abx therapy

CATHETER-ASSOCIATED BACTERIURIA

How common is catheter-associated bacteriuria?

- most common nosocomial infection } accounts for ~40%
- inevitable & occurs at ~10% per day of catheterization } febrile episodes occur only 1 per 100 days
- usually asymptomatic

What are the RFs for catheter-associated bacteriuria?

- duration of catheterization
- female gender
- absence of systemic Abx
- poor catheterization technique

What is the route of infection in patients with catheter-associated bacteriuria?

- introduced with initial catheterization } urethral bacteria or poor technique
- retrograde colonization from Foley bag } intraluminal route to bladder

What are the causative pathogens of catheter-associated bacteriuria?

- **bacteria w/in urine can differ from bacterial biofilm on catheter**
 - Pseudomonas & Proteus common biofilm pathogens
- **E coli still most common**
- Pseudomonas, Proteus, and enterococcus more common
- polymicrobial bacteriuria very common

What is the management of catheter-associated bacteriuria?

- **no Abx recommended if catheter to stay indwelling for >3-4 days**
- **Abx treatment only if symptomatic UTI**
 - send urine C&S before initiating Abx therapy
 - stop within 48hrs of resolution of infection
 - catheter should be changed
- Abx around time of catheter change or removal recommended for 2-3 days

MANAGEMENT OF UTIs IN PATIENTS WITH SPINAL CORD INJURY

How common are UTIs amongst those with SCI?

- roughly 33% have bacteriuria at any one time
- **UTI is the most common cause of fever in SCI patient**

What are the RFs associated with SCI that predispose patients to UTIs?

- | | |
|---|--|
| - impaired voiding | - increased incidence of stones |
| - overdistention of the bladder | - decreased fluid intake |
| - elevated bladder pressure | - poor hygiene |
| - increased risk of urinary obstruction | - perineal colonization |
| - VUR | - local tissue trauma (eg ulcers) |
| - instrumentation | - reduced host defense associated w/ chronic illness |

Why is CIC preferred over indwelling catheterization in SCI patients?

- lower incidence of bacteriuria
- less complications with fever, bacteremia, and local infections (eg prostatitis)
- reduces incidence of stones
- maintains low bladder pressures
- S/P catheters next best, followed by condom catheters

How do SCI patients with UTIs usually present?

- **most are asymptomatic**
- don't have irritative symptoms because of a loss of sensation
- often complain of flank or back pain or abdo discomfort
- leakage between catheterizations
- increased spasticity
- malaise, lethargy
- cloudy, smelly urine
- UTI is the most common cause of fever in SCI patients
- u/a usually shows bacteriuria and pyuria } pyuria alone may be from catheterizations

What are the causative pathogens in SCI patients with UTI?

- E coli found in ~20%
- **Enterococci, Proteus mirabilis, and Pseudomonas much more common**
- Klebsiella, Serratia, Candida are also common
- Providencia stuartii rarely found outside long-term catheterized GU tract
- often have polymicrobial infections

What is the management of UTIs in SCI patients?

- **ONLY SYMPTOMATIC PATIENTS NEED ABX**
- **urine culture MUST be obtained BEFORE administration of ABx**
 - high rate of resistance and often diverse flora
- for afebrile patients, oral fluoroquinolone is Abx of choice
- indwelling catheters should be changed
- if febrile, patients should be admitted and started on iv Abx (eg amp + gentamicin/ceftriaxone)
- if no clinical improvement by 24-48hrs, then reculture and adjust Abx based on initial urine C&S
 - consider imaging to r/o obstruction, stones, abscess
- 4-5days Abx for most, 10-14days if febrile
- **post-Abx cultures NOT RECOMMENDED because of high rate of re-colonization**
 - **except with urease-producing bacteria**
- SCI patients w/ recurrent UTIs need imaging & UDS testing with review of sterile techniques
- **NO ABX PROPHYLAXIS RECOMMENDED**

What is the risk of bladder cancer with chronically catheterized patients?

- risk of developing **SCC of bladder** with chronic catheter or chronic infections
- risk evident usually after 5-10yrs
- chronic inflammation of mucosa may be carcinogenic stimulus
- nitrosamines produced in infected urine may also play a part

FUNGURIA

What are the RFs associated with funguria?

- indwelling catheters
- Abx therapy
- DM
- hospitalization
- immunosuppressed states

What are the common fungal pathogens?

- **Candida albicans accounts for ~50%**
- Candida glabrata is 2nd most common (10-15%)

How does funguria usually present?

- **asymptomatic colonization is common**
- **UTI is usually symptomatic with irritative voiding symptoms and pyuria**
- renal or perinephric abscesses may result from funguria } present like pyelonephritis
 - fungus balls (fungal bezoars) may also result from fungal infection but don't always present like pyelo (pt may be asymptomatic)
- cultures of 10, 000 or 15, 000 cfu/mL are considered +ve
- may see pseudohyphae on microscopy

What is the management of funguria?

→ **treatment of ONLY SYMPTOMATIC FUNGURIA RECOMMENDED**

- 1) remove or change catheter (if present), stop antibacterial Abx, and improve pt's nutritional status
- 2) reculture
 - if reculture is -ve then OBSERVE
 - if reculture is +ve then needs assessment
- 3) bloodwork & assess upper tracts (U/S, CT)
 - **if systemic manifestations (fever, WBC count, etc) or other culture sites +ve then IV FLUCONAZOLE OR AMPHOTERICIN B**
 - start at 1mg then increase by 5mg to ~0.5-1.0mg/kg (max 50mg/day)
 - **if no upper tract abnormalities then PO FLUCONAZOLE for 2-3 weeks**
 - OR BLADDER IRRIGATION for 1 week
 - bladder irrigation not preferred any more
 - 50mg of amphotericin B in 1L sterile water over 24hrs
 - 200mg fluconazole x1day, then 100mg po od for 2 weeks
 - if persistent infection then IV FLUCONAZOLE OR AMPHOTERICIN B
 - if +ve filling defect then culture ureteral/renal unit
- 4) if ureteral or renal unit culture +ve then need
 - a) antifungal irrigation by NT or ureteral catheter with amphotericin B +/- removal of fungal bezoar
 - b) IV FLUCONAZOLE OR AMPHOTERICIN B

What are the S/E's of po fluconazole?

- renal clearance } renal dosing REQUIRED
- N/V
- abdo pain
- diarrhea
- H/A
- rash
- rarely liver failure
- increases effects of coumadin

What are the S/E's of iv amphotericin?

- biliary clearance (usually no renal dosing required) } it is a nephrotoxic drug though
 - liposomal formulation has less side effects and is less nephrotoxic
- can see histaminic rxn few hrs after dosing } fevers, chills, rigors, hypoTN, tachypnea, dyspnea
- "AAA MMM PPP HHH O B"
 - Anaphylaxis
 - Anemia
 - Arrhythmias
 - Myalgia/flu-like symptoms (fever, chills, etc)
 - Microcephaly (only congenital anomaly)
 - Multi-organ failure (liver, etc)
 - Pain
 - Phlebitis
 - Platelets low (thrombocytopenia)
 - HypoK
 - HypoCa
 - HypoMg
 - Ototoxicity
 - Bean toxicity (nephrotoxicity)

OTHER INFECTIONS

What is Fournier's Gangrene?

- necrotizing fasciitis of the genitalia & perineum
- often abrupt onset of a rapidly fulminating genital gangrene } can be indolent onset
- source of infection is most commonly from skin, urethra, or rectal regions
- bacteria pass through Buck's fascia and **spread along dartos fascia of scrotum & penis, Colles' fascia of perineum, and Scarpa's fascia of anterior abdo wall**

What are the RFs for Fournier's gangrene? }} DAMPPP SCROOTI

- | | |
|---------------------------|-------------------------------------|
| - DM | - Surgery in local area |
| - Alcohol abuse | - CIC (urine extravasation) |
| - Malnutrition | - Roids |
| - Perianal disease | - Old age |
| - Paraphimosis | - Obesity |
| - PVD | - Trauma |
| | - Immunosuppression (eg HIV) |

How does Fournier's gangrene usually present?

- pt usually has hx of recent perineal trauma, instrumentation, urethral stricture associated with STD or urethrocutaneous fistula
- may have hx of perirectal disease } fissures, pain, rectal bleeding, etc
- usually starts with local cellulitis that spreads deeper
 - **most commonly mixed bacterial growth } E coli most common single pathogen**
- often presents with pain, fever, and systemic toxicity (mental status changes, tachypnea, tachycardia)

What lab & imaging features may suggest a Dx of Fournier's gangrene?

- | | |
|-----------------------|---|
| → blood work | → imaging |
| - anemia | - plain film Xray may show subcutaneous air |
| - elevated creatinine | - U/S or CT may also be good to demonstrate air |
| - hypoNa | |
| - hypoCa | |

What is the management of Fournier's gangrene?

- prompt Dx is critical
- ABCs
- iv fluids
- routine blood work
- culture urine, blood, and site of infection
- broad spectrum Abx } ampicillin + ceftriaxone + flagyl
- immediate surgical debridement
 - all necrotic skin, fascia, fat must be excised & wound left open
 - repeat debridement in 24-48hrs PRN
 - orchiectomy almost never required b/c testes have own blood supply
 - place testicles in thigh pouch or wrap in moist NS-soaked gauze
- S/P tube if urethral trauma or extravasation suspected
- colostomy if colonic or rectal communication
- hyperbaric O2 has been shown to improve outcomes
- once wound has healed, may need reconstruction to close defect if large eg myocutaneous flap

What are the outcomes of treatment for Fournier's gangrene?

- **mortality rate is ~20%** } higher if DM, EtOH'ic, and those w/ colorectal source of infection

What are periurethral abscesses?

- life-threatening condition of M urethra and periurethral tissues
- frequently a result of **gonorrhea, urethral strictures, or urethral CIC**
- urine is source of infection } usually gram -ves, enterococci, and anaerobes

How do periurethral abscesses usually present?

- initially localized by Buck's fascia to a small area
- once it penetrates through Buck's, it can spread rapidly from buttocks posteriorly to clavicles superiorly
- usually have scrotal swelling and fever
- sometimes have AUR, spontaneously draining abscess, or urethral symptoms
- urinalysis shows bacteriuria and pyuria

What is the management of a periurethral abscess?

- immediate S/P drainage
- iv hydration
- iv ABx } ampicillin + gentamicin/ceftriaxone
- wide debridement

Chapter #9 – Prostatitis, Orchitis, Epididymitis

PROSTATITIS

How common is prostatitis?

- **most common urologic Dx in men <50yrs of age**
- 3rd most common urologic Dx in men >50yrs of age (BPH, PCa)
- represents ~8% of male outpatient visits to the urologist } prevalence varies with geography
- more common in the 20-49 age range and if >70yrs old
- 2-10% of men currently experience prostatitis-like symptoms
- 10-15% of men have had a Dx of prostatitis

What is the histopathology of prostatitis?

- ↑'d number of inflammatory cells within the prostatic parenchyma
- **stromal lymphocytic infiltrate immediately adjacent to prostatic acini**
 - **most common pattern**
 - varies from scattered lymphocytes to dense lymphoid nodules
 - often coexists with periglandular inflammation
- can also see infiltrates of inflammatory cells in glandular epithelium and lumen
 - intraepithelial inflammatory cells are neutrophils, lymphocytes, and/or macrophages
 - luminal inflammatory cells are usually neutrophils and macrophages
- prostatic stones may be present
 - can contribute to inflammation by obstructing central prostate ducts

What is the significance of granulomatous prostatitis?

- non-specific and variable histologic pattern
 - heavy lobular, mixed, inflammatory infiltrates } histiocytes, lymphocytes & plasma cells
 - small, discrete granulomas or well-defined granulomas
- **common consequence of prostate surgery, BCG therapy, or systemic TB**

What is the Traditional classification of prostatitis?

- described by Drach et al ('78) based on Meares-Stamey 4-glass test
- type 1 } acute bacterial prostatitis
 - purulent prostatic fluid (VB3) + systemic signs + cultured bacteria
- type 2 } chronic bacterial prostatitis
 - purulent prostatic fluid (VB3) + cultured bacteria + NO systemic signs
- type 3 } non-bacterial prostatitis
 - microscopic WBC in prostatic fluid (VB3) + NO bacteria + NO systemic signs
- type 4 } prostatic dysplasia
 - symptoms only
 - NO WBCs in prostatic fluid (VB3) + NO bacteria + NO systemic signs

What are the potential causes of prostatitis? } } } "MIMIC Dick PAIN"

- 1) **Microbiologic causes**
 - **bacteria cultured in only ~10% of cases**
 - gram -ve } Enterobacteriaceae family (most common cause of bacterial prostatitis)
 - *E. coli* (most common), *Pseudomonas*, *Serratia*, *Klebsiella*, *Enterobacter*
 - } P-fimbria (P-pili), type 1 fimbria, biofilm are urovirulence factors that play a role in pathogenesis of bacterial prostatitis
 - gram +ve } mainly Enterococcus
 - } others may be involved also (*S. aureus*, *S. saprophyticus*, etc)
 - these are currently considered category III
 - *Corynebacterium* } hard to culture, gram-variable pleomorphic coccobacillary rods
 - } could play a role
 - these are currently considered category III
 - *Chlamydia trachomatis* } might be an etiologic agent
 - *Ureaplasma urealyticum* } might be an etiologic agent
 - others } candida, viruses, non-culturable micro-organisms
- 2) **Intraprostatic ductal reflux**
 - may be the most important etiologic mechanism involved in chronic bacterial and non-bacterial inflammation
- 3) **Multifactorial cause**
- 4) **Immunologic alterations**
 - immunologic cascade, regardless of initiating event, plays important role
- 5) **Chemically-induced inflammation**
 - refluxing urine causes inflammation
- 6) **Dysfunctional voiding**
 - anatomic or neurophysiologic obstruction
- 7) **Psychological cause**
 - important role in development or exacerbation
 - psychosomatic disorder
- 8) **Altered prostatic host defense ("CAT PUBES")**
 - Catheters (indwelling)
 - Anal sex (unprotected)
 - TRUS/TURP
 - Phimosis
 - UTIs
 - Blood groups (certain types more susceptible)
 - Epididymitis (acute)
 - Secretory dysfunction of prostate
 - low fructose, citric acid, Zn, Mg, Ca or increased pH, C3, LDH-5
- 9) **Interstitial cystitis-like cause**
- 10) **Neural dysregulation/pelvic floor musculature abnormalities**
 - dissociation between CNS and pelvic floor muscles
 - pain at pelvic musculature attachment sites (sacrum, coccyx, ischial tuberosity, pubic rami, etc)
 - myofascial trigger points
 - pudendal nerve entrapment

What is the new NIH classification of prostatitis?

→ now the best system for research and clinical practice

- category I } acute bacterial prostatitis
 - purulent prostatic fluid (VB3) + systemic signs + cultured bacteria
- category II } chronic bacterial prostatitis
 - purulent prostatic fluid (VB3) + cultured bacteria + NO systemic signs
 - requires at least 10-fold increase in bacteria in EPS/VB3 specimen compared to VB1/VB2
- category III } chronic GU PAIN in absence of uropathogenic bacteria localized to prostate using standard methodology [**“chronic pelvic pain syndrome (CPPS)”**]
 - IIIA } inflammatory CPPS
 - pain + **WBCs** in VB3 urine or semen
 - need >5-10 WBCs per HPF
 - IIIB } non-inflammatory prostatitis (prostadynia)
 - pain but **NO significant WBCs** in VB3 urine or semen
 - <5-10 WBCs per HPF
- category IV } asymptomatic inflammatory prostatitis
 - NO PAIN + WBCs +/- bacteria in VB3 urine or semen or tissue Bx's

How does prostatitis usually present?

- 1) category I } acute onset of pain (perineal, S/P, genital) + LUTS + systemic febrile illness
 - can have frank septicemia
 - ~5% progress on to chronic bacterial prostatitis
- 2) category II } recurrent UTI history is common
 - } may be asymptomatic between acute episodes or may present with long hx of a CPPS
- 3) category IIIA and IIIB } pain is predominant symptom (perineal, S/P, genital, low back)
 - pain during or after ejaculation is prominent
 - } can also have LUTS and ED
 - } can't distinguish IIIA from IIIB
 - } “chronic” if symptoms last >3months
- 4) category IV } no symptoms by definition
 - } present with BPH, elevated PSA, PCa, infertility

What is the NIH-CPSI?

- National Institutes of Health – Chronic Prostatitis Symptom Index
 - population-based and validated } useful research & clinical tool for evaluating CPPS patients
 - measures symptoms and QOL of chronic prostatitis
 - **9 questions looking at 3 domains**
 - a) **pain (4)** } location, frequency, severity
 - b) **urinary function (2)** } irritative, obstructive
 - c) **QOL/impact (3)**
- 6points or 25% decrease constitutes significant improvement

What is the work-up for prostatitis?

Table 9-2 -- Suggested Evaluation of a Man with CPPS[*]

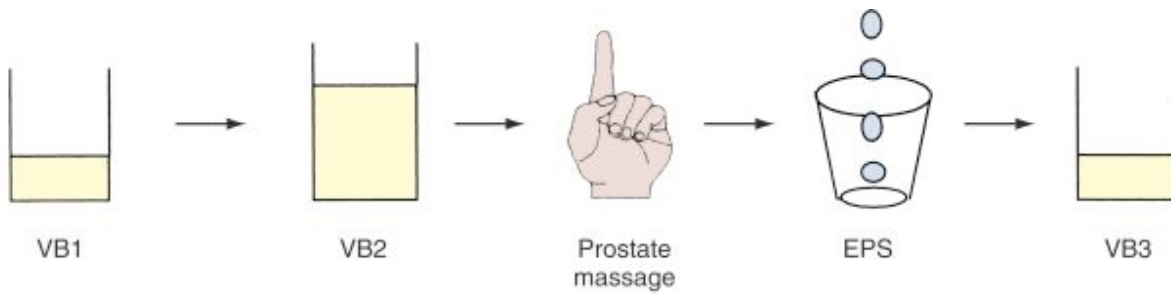
<i>Mandatory</i>
History
Physical examination, including digital rectal examination
Urinalysis and urine culture
<i>Recommended</i>
Lower urinary tract localization test
Symptom inventory or index (NIH-CPSI)
Flow rate
Residual urine determination
Urine cytology
<i>Optional</i>
Semen analysis and culture
Urethral swab for culture
Pressure flow studies
Video urodynamics (including flow electromyography)
Cystoscopy
Transrectal ultrasound
Pelvic imaging (ultrasound, CT, MRI)
Prostate-specific antigen

→ “HUU, SQUU”

- Mandatory } History & Physical
- } Urinalysis
- } Urine C&S
- Recommended } Stamey test
- } Questionnaire (CPSI)
- } Uroflow & PVR
- } Urine cytology

What other tests have been used in the evaluation of prostatitis?

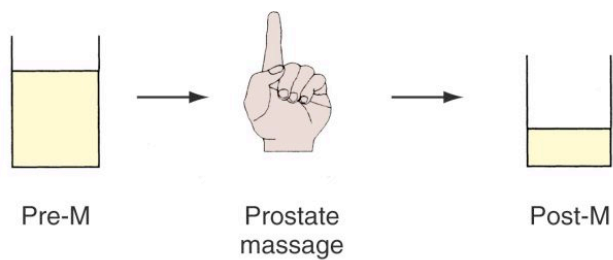
- mainly in research settings only
- serum immunologic testing (antibodies, IL-1, etc)
- Zn levels
- +ve rRNA-based signals



4-Glass test (Meares-Stamey test)

Classification	Specimen	VB ₁	VB ₂	EPS	VB ₃
CAT II	WBC	—	+/-*	+	+
	Culture	—	+/-*	+	+
CAT IIIA	WBC	—	—	+	+
	Culture	—	—	—	—
CAT IIIB	WBC	—	—	—	—
	Culture	—	—	—	—

→ MEARES-STAMEY 4-GLASS TEST



2-Glass test (PPMT)

Classification	Specimen	Pre-M	Post-M
CAT II	WBC	+/-*	+
	Culture	+/-*	+
CAT IIIA	WBC	—	+
	Culture	—	—
CAT IIIB	WBC	—	—
	Culture	—	—

→ 2-GLASS TEST

List medical Rx options for prostatitis? } } } “AAA Meds Help Alleviate Prostatitis Problems”

- 1) **Abx**
 - good initial Rx } up to 40% improvement in symptoms (even when CPPS)
 - ?placebo effect
 - ?eradication of non-cultured bugs
 - ?independent anti-inflammatory effects of some Abx's
 - } initial acute infection
 - amp + gent
 - 2nd or 3rd generation cephalosporin
 - fluoroquinolone
 - } chronic bacterial prostatitis
 - trimethoprim \ optimal duration unknown
 - fluoroquinolone / → minimum 4-12weeks
 - NOT RECOMMENDED for previously Rx'd men with non-bacterial CP/CPPS of long duration
- 2) **α-blockers (eg flomax)**
 - **moderate benefit on RCTs**
 - may improve outflow obstruction and diminish intraprostatic ductal reflux
 - best results if recent-onset of disease, no/little hx of previous treatments, and after >6wk course of α-blockers (stop if no benefit after 12 wks)
 - combination therapy with Abx or anti-inflammatories may improve outcomes
- 3) **Anti-inflammatories**
 - **modest benefit on RCTs**
 - decreases inflammation w/in prostate (NSAIDs, steroids, immunosuppression)
 - rofecoxib, celecoxib, po pentosan polysulfate, prednisone, etc
 - long term therapy not recommended
- 4) **Muscle relaxants (eg baclofen)**
 - no good RCTs
 - addresses possible etiology of neural dysregulation/pelvic floor musculature abN'ities
 - some mild benefits shown
- 5) **Hormonal therapies (eg finasteride, estrogens)**
 - no good RCTs
 - regression of glandular tissue, improved voiding parameters, reduced intraprostatic ductal reflux
 - NOT RECOMMENDED as monotherapy, except in men with associated BPH
- 6) **Allopurinol**
 - no benefit
- 7) **Phytotherapies**
 - **modest benefit on RCTs**
 - 5ARI activity, α-blocker activity, and anti-inflammatory properties
 - *Serenoa repens* (saw palmetto), cernilton (bee pollen), Quercetin (flavonoid)
- 8) **Pentosan polysulfate**

List non-medical treatments for prostatitis } SAME Bullshit Procedures for Prostatitis Problems

- 1) **Surgery**
 - minimally invasive Rx } balloon dilation, TUNA, TUMT (promising)
 - S/P tube for long term relief of BOO } usually CIC or short-term catheter adequate
 - transurethral incision of prostatic abscess seen on TRUS or CT
 - TUI of BN } if UDS evidence of BN obstruction
 - TURP } for refractory category II prostatitis
- 2) **Acupuncture** (investigational)
- 3) **Massage of prostate**
 - historical treatment
 - some improvement has been demonstrated
 - frequent ejaculations may achieve same results
- 4) **Ejaculate frequently**
- 5) **Biofeedback**
- 6) **Psychologic support**
 - used as part of multi-dimensional care
- 7) **Pelvic/perineal Floor Massage Training + myofascial trigger point release**
 - eg heat therapy, physiotherapy massage, stretching, anesthetic injections, etc
- 8) **Pudendal nerve entrapment therapy**

\ /
investigational
(more research
required)

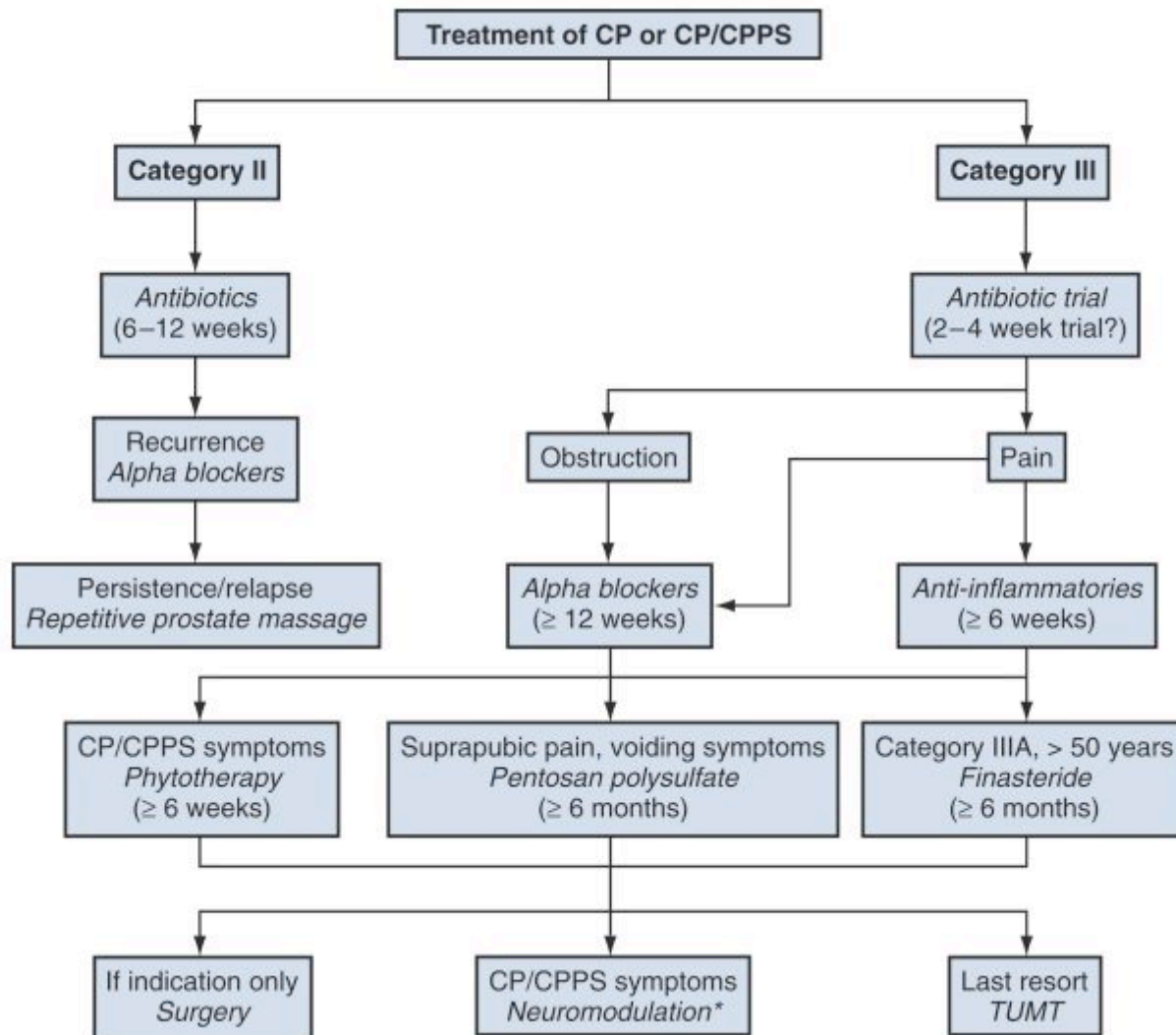
What are the potential etiologies of myofascial trigger points in the perineum or pelvis?

- mechanical abnormalities in the hip and lower extremities
- chronic urinary holding patterns (dysfunctional toilet training)
- sexual abuse
- repetitive minor trauma
- constipation
- unusual sexual activity
- recurrent infections or surgery
- stress and anxiety

Which ABx's concentrate well in the prostate, and which do not?

Good intraprostatic concentrations	Poor intraprostatic concentrations
- TMP	- SMX
- fluoroquinolones	- ampicillin
	- carbenicillin
	- aminoglycosides

*** most Abx's get into prostate well in acute infection ***



→ ALGORITHM FOR CHRONIC PROSTATITIS/CP/PPS

RELATED CONDITIONS

Seminal Vesiculitis

What is seminal vesiculitis?

- usually occurs as a **consequence of acute or chronic bacterial prostatitis or acute epididymitis**
- can present with SV abscesses
- Dx made clinically with +ve ejaculate culture
- traditional imaging was seminal vesiculography } now with CT, TRUS, MRI, or
99mTc-ciprofloxacin radioisotope scan

Rx → Abx +/- transrectal aspiration
→ seminal vesiculectomy } open vs lap

Orchitis

How do you classify orchitis (CHART)?

- 1) acute bacterial orchitis
 - secondary to UTI
 - secondary to STD
- 2) acute non-bacterial infectious orchitis
 - viral
 - fungal
 - parasitic
 - Rickettsial
- 3) acute non-infectious orchitis
 - idiopathic
 - traumatic
 - autoimmune
- 4) chronic orchitis \ persists for
- 5) chronic orchialgia / >6wks

What are the infectious causes of orchitis?

- 1) acute bacterial } secondary to local spread of ipsilateral epididymitis
 - } UTIs and STDs
 - *E. coli*, *Pseudomonas*, *Klebsiella*, enterococcus, etc
 - *Neisseria gonorrhoeae*, *C. Trachomatis*, *Treponema pallidum*
 - can also see mycobacterium (TB more common than leprosy)
- 2) acute non-bacterial } mumps is most common cause of viral orchitis
 - can also get EBV (mono) orchitis
 - **usually don't see associated epididymitis with viral orchitis**
 - } candidiasis, aspergillosis, histoplasmosis, coccidioidomycosis, etc
 - } parasitic orchitis rare in Western world
 - filariasis in Africa, Asia, S. America

How does acute infectious orchitis usually present?

- recent onset of testicular pain often with abdo discomfort, N/V, etc
- may have associated parotitis (mumps - paramyxovirus), LUTS (UTIs), or urethritis (STDs)
- usually unilateral } more likely viral if bilateral
- erythematous and edematous hemiscrotum } may have associated hydrocele
- febrile +/- toxic

What is involved in the work-up of orchitis?

- 1) History & physical } r/o torsion, prostatitis, urethritis, malignancy
- 2) Lab tests
 - urine R&M + urine C&S
 - +/- urethral swab (if STD suspected)
- 3) imaging
 - scrotal U/S } r/o torsion & malignancy (in chronic orchitis/orchalgia)

What is the management of orchitis?

- bed rest + scrotal support
- hydration + antipyretics + anti-inflammatories + pain meds
- Abx } specific for UTI, prostatitis, or STD
- spermatic cord blocks for severe pain or chronic orchitis/orchalgia
- percutaneous or open drainage if abscess forms } rare

Epididymitis

How do you classify epididymitis (CHART)?

- 1) acute bacterial epididymitis
 - secondary to UTI
 - secondary to STD
- 2) acute non-bacterial infectious epididymitis
 - viral
 - fungal
 - parasitic
- 3) acute non-infectious epididymitis
 - idiopathic
 - traumatic
 - autoimmune
 - amiodarone-induced
 - associated with a known syndrome (eg Behcet's disease)
- 4) chronic epididymitis
- 5) chronic epididymyalgia

What are the infectious causes of epididymitis?

- 1) acute bacterial } usually from spread of infection from bladder, urethra, or prostate via ejaculatory ducts & vas deferens
 - in kids, often due to UTI +/- underlying GU anomaly
 - in older men, usually due to BOO
 - in younger, sexually active men, usually due to STDs (gonorrhea & Chlamydia)
- } most cases also involve ipsilateral testis
- 2) acute non-bacterial } viral, fungal, parasitic organisms have all been implicated
- 3) chronic epididymitis } inadequately treated acute epididymitis, recurrent epididymitis, or in association with other diseases (eg Behcet's disease)

How does acute infectious epididymitis usually present?

→ very similar to orchitis } most present as epididymo-orchitis

- tenderness may be localized to epididymitis } tail is first to be tender
- spermatic cord may be tender and swollen

What is involved in the work-up of epididymitis?

- 1) History and physical } r/o torsion, prostatitis, urethritis, malignancy
- 2) Lab tests
 - urine R&M + urine C&S
 - +/- urethral swab (if STD suspected) } gram -ve diplococci = gonorrhea
 - } only WBCs = likely Chlamydia in 2/3
- 3) imaging
 - scrotal U/S } r/o torsion & malignancy (in chronic epididymitis/epididymyalgia)
 - abdo/pelvic U/S + VCUG in kids

What is the management of epididymitis?

- scrotal supports + anti-inflammatories + pain meds
- Abx for UTI (14day course), STD (single dose), etc
- +/- nerve blocks for severe pain or chronic epididymitis/epididymyalgia
- 4-6 wk trial of ABx for possible bacterial pathogens and Chlamydia for chronic epididymitis

What are the potential complications of acute epididymitis?

- abscess formation
- testicular infarction
- chronic pain
- infertility

Chapter #10 – Painful Bladder Syndrome/Interstitial Cystitis and Related Disorders

DEFINITION

What is the ICS definition of PBS?

- “S/P pain related to bladder filling, accompanied by other symptoms such as increased daytime & night time frequency, in the absence of proven UTI or other obvious pathology”
- **“pain/pressure/discomfort” is the primary component of PBS/IC**

What is the ICS definition of IC?

- reserved for patients with “typical cystoscopic & histological features” (undefined)
- should be considered part of PBS/IC

What is the 1990 NIDDK diagnostic criteria for IC (CHART)?

- National Institute of Diabetes, Digestive, and Kidney disease
- 1) either classic Hunner’s ulcer OR glomerulations (distention to 80-100 cm H₂O x 1-2mins; present in ≥3 quadrants of bladder with ≥10 glomerulations per quadrant) on cystoscopy
- AND
- 2) pain associated with either the bladder OR urinary urgency

What are the 1990 NIDDK exclusion criteria for IC (CHART)?

- bladder capacity >350cc on awake cystometry (gas or liquid)
- absence of intense urgency with bladder filled to 100cc (gas) or 150cc (liquid)
- evidence of involuntary contractions on CMG
- symptoms for duration <9months
- absence of nocturia
- symptoms relieved by ABx, urinary antiseptic agents, anticholinergics, or anti-spasmodics
- daytime frequency <8x per day
- a diagnosis of bacterial cystitis or prostatitis within last 3 months
- bladder or ureteral stones
- active genital herpes
- uterine, cervical, vaginal, or urethral cancer
- urethral diverticulum
- cyclophosphamide or any type of chemical cystitis
- TB cystitis
- radiation cystitis
- bladder tumours (benign or malignant)
- vaginitis
- age <18yrs

How common are glomerulations and Hunner’s ulcer?

- glomerulations } low sensitivity and specificity
- Hunner’s ulcer } only present in <5%

What is the ICDB criteria for diagnosing IC (CHART)?

- Interstitial Cystitis DataBase
- more symptom based than NIDDK
- >18yrs of age
- urgency, frequency or pain for >6months duration
- daytime frequency ≥ 7 x per day
- no hx of current GU TB
- no hx of urethral cancer
- no hx of bladder cancer, high-grade dysplasia, or CIS
- no hx of PCa
- no occurrence of ovarian, vaginal, or cervical cancer in last 3 yrs
- no current vaginitis, clue cell, trichomonas, or yeast infections
- no bacterial cystitis in last 3 months
- no active herpes in last 3 months
- no Abx for UTIs in last 3 months
- no hx of cyclophosphamide
- no radiation cystitis
- no neurogenic bladder dysfunction (eg SCI, stroke, Parkinson's, MS, spina bifida, DM, etc)
- no BOO (based on UDS)
- no bacterial prostatitis in last 6 months
- no bladder, ureteral, or urethral stones in last 3 months
- no urethritis in last 3 months
- no hx of urethral dilation, CMG, cystoscopy under GA, or bladder Bx in last 3 months
- no hx of bladder augment, cystolysis, or neurectomy
- no urethral stricture <12Fr
- 60% of those diagnosed with IC by the ICDB criteria would NOT have been diagnosed by NIDDK criteria

How common is detrusor overactivity in PBS/IC patients?

- found on UDS in ~14%
- similar to general population

EPIDEMIOLOGY

Why is it difficult to compare prevalence of PBS/IC?

- no accepted definition
- no validated diagnostic marker
- questions regarding etiology & pathophysiology

What are some of the population-based findings of PBS/IC?

- median age at onset is 40yrs
- late deterioration of symptoms is unusual
- **~50% temporary spontaneous remission rate } mean duration is ~8months**
- **hx of childhood bladder problems** is 10x more common in IC patients vs controls
- hx of UTIs is 2x more common in IC patients
- higher propensity in Jews
- IC patients have a lower QOL than dialysis patients
- **F:M ratio = 5:1**
- ~10% have severe symptoms
- **high incidence of comorbidities such as depression, chronic pain, anxiety**
- more common in US than Scandinavia & Japan
- **benign condition } not pre-malignant**

What are the most common conditions associated with PBS/IC? }} “ASS IF Vestibulitis”

- **Allergies } MOST COMMON (>40%)**
- **SLE**
- **Sjogren's syndrome**
- **IBS/IBD**
- **Fibromyalgia**
- **vulvar vestibulitis/focal vulvitis**

ETIOLOGY

What are the proposed theories on the cause of PBS/IC? } } “My Infected ANUS Leaks”

→ likely multifactorial etiology that acts predominantly through one or more pathways

- 1) **Mast cell activation** } elevated in IC detrusor muscle and urothelium (histamine release)
 } reported to be a pathognomonic marker
- 2) **Infection of bladder wall (chronic)** } weak evidence at best
- 3) **Autoimmune disorder** } anti-nuclear Ab's, response of symptoms to steroids
- 4) **Neurogenic inflammation** } evidence of increased neural changes in IC
 } may be result of leaky epithelium/GAG + mast cell activation
- 5) **Urine toxicity** } induction of toxic, allergic, or immunologic inflammation
 } increased anti-proliferative factor (APF; a frizzled 8 protein) in IC urine
- 6) **others** } Stress, estrogen/female hormones, pelvic floor dysfunction, psychologic
- 7) **"Leaky epithelium"** } abN epithelium and/or GAG layer

What are the major classes of GAG?

- hyaluronic acid
- heparin sulfate
- heparin } **only one not found on bladder surface**
- chondroitin 4-sulfate, chondroitin 6-sulfate
- dermatan sulfate
- keratan sulfate

List characteristic clinical features of non-nociceptive pain (CHART).

- 1) pain out of proportion w/ degree of pathology found (or there is no pathology found)
- 2) noxious stimuli causes pain greater or more unpleasant than expected (hyperalgesia)
- 3) normally non-noxious stimuli may result in pain (allodynia)
- 4) extent of pain boundary is greater than would be expected based on site of original pathology

PATHOLOGY

What is the role of histopathology in making the diagnosis of PBS/IC?

- no pathognomonic histology
 - can have pathology “consistent with diagnosis of IC”
 - severely abN pathology might be associated with poor prognosis
- } **main role of pathology is to**
/ **r/o other possible etiologies**

What are some findings on pathology that might suggest PBS/IC?

- normal
- increased number of activated mast cells (on tryptase stain)
- ulcers } denuded urothelium extending into LP
- submucosal inflammation or edema
- submucosal hemorrhage
- granulation tissue
- none are consistent or specific

DIAGNOSIS

List chronic visceral pain syndromes that affect the urogenital & rectal area?

- PBS/IC
 - vulvodynia
 - orchialgia
 - penile pain
 - rectal pain
- \ } poorly understood
/

How is PBS/IC diagnosed?

- **Dx of exclusion based on symptoms** } chronic pain/pressure/discomfort associated with the bladder, usually accompanied by urinary frequency, in the absence of any identifiable cause
- IC symptom scales are used mainly to evaluate severity of symptoms and to monitor disease progression/regression with or without treatment } not validated as diagnostic criteria
- **NIDDK and ICDB criteria no longer used for Dx** } research purposes

What are some of the other conditions that must be ruled out before making the Dx of PBS/IC?

- carcinoma (bladder, urethra, prostate, uterus, vagina, vulva, etc)
- infections (UTIs, STDs, TB, etc)
- voiding dysfunction
- meds-induced non-bacterial cystitis (eg cyclophosphamides, ASA, NSAIDs, allopurinol, etc)
- urethral abnormalities (strictures, diverticulum, etc)
- eosinophilic cystitis
- malacoplakia
- schistosomiasis
- scleroderma
- detrusor endometriosis

What are some urinary markers of PBS/IC?

- 1) mast cells
 - 2) GAG excretion
 - 3) histamine levels
 - 4) NOS levels
 - 5) eosinophilic cationic protein
 - 6) **anti-proliferative factor (APF) levels** }
- \ } all are of debatable clinical utility
/
- most accurate w/ highest sensitivity & specificity of the various possible markers**

What is the intravesical KCl test?

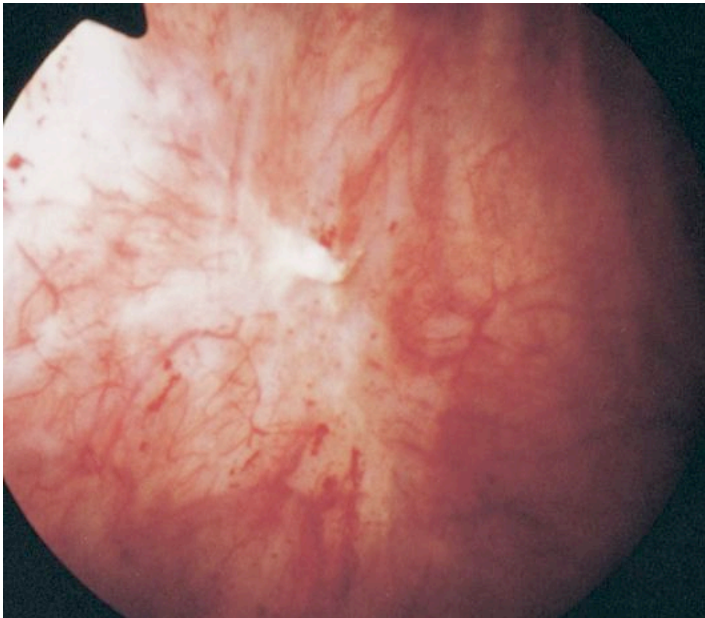
- Parsons et al
- sensory nerve provocative ability of NS vs KCl using a 400mEq/L KCl solution
- **pain and provocation of symptoms = +ve test** } **suspicious for IC**
 - may indicate abN “leaky” urothelium or hypersensitive sensory nerves
- not diagnostic but may stratify which patients might respond to certain Rx (eg GAG replacement)
- rare to have false +ve’s } good specificity
- high false –ve rate } poor sensitivity

What is the Ddx of a +ve intravesical KCl test? } } } “I CROUP”

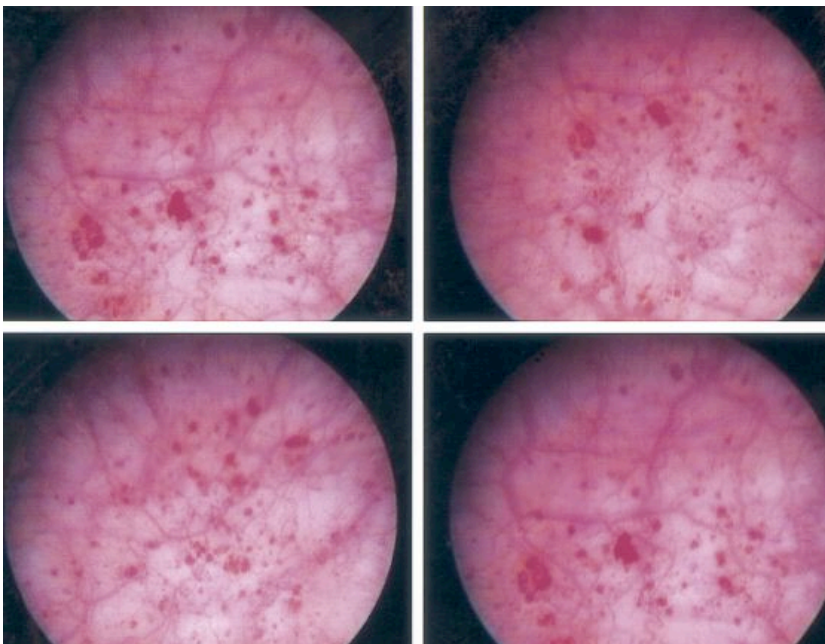
- IC
- CPPS } men and women
- Radiation cystitis
- OAB
- UTI
- Prostatitis (chronic)

What is the DDx of bladder glomerulations? } } } "DIRECT"

- Diversion
- IC/PBS
- Radiation
- ESRD with low urine output (dialysis)
- CIS
- Toxic chemotherapy/chemicals



→ HUNNER'S ULCER



→ GLOMERULATIONS

CLINICAL SYMPTOM SCALES

What are the 3 main PBS/IC symptom scales? } } } “WOP”

- 1) Univ. of Wisconsin IC Scale } 25 total questions with 7 specific PBS/IC questions
→ score 0 to 6 (Likert scale)
} not validated for identification or diagnosis of PBS/IC
→ does correlate with PBS/IC
} does address some QOL issues
- 2) O’Leary-Sant IC Symptom Index } 4 questions per index specific to PBS/IC
and IC Problem Index → urgency, frequency, nocturia, bladder pain (Likert scale)
- total of 8 questions
} validated to identify PBS/IC
→ correlates strongly with PBS/IC
- 3) Pelvic Pain and Urgency/Frequency (PUF) } 8 questions
Symptom Scale → frequency, nocturia, sexual function x2, bladder or
pelvic pain x2, urgency x2 (Likert scale)
- also addresses degree of bother
} face-validity may be poor

ASSESSING TREATMENT RESULTS

Why is it difficult to assess treatment outcomes for PBS/IC?

- 50% incidence of temporary remission (unrelated to Rx) with mean duration of ~8 months
- little to no long-term changes in average symptom severity
- improvements and/or changes may be from regression to the mean or placebo effect & not necessarily from intervention effect
- few IC treatments have been subjected to placebo-controlled trials
- statistical significance DOES NOT = clinical significance in all situations

CONSERVATIVE THERAPY

What are some of the conservative therapies used for PBS/IC?

→ **there is currently NO evidence that early Rx affects the natural hx or course of PBS/IC**
→ **“AWE, Poor Bladder’s MAD”**

- 1) ABx (empiric course) } only if patient hasn’t had a trial already
- eg doxycycline
- 2) Watchful waiting/observation
- if symptoms are tolerable
- 3) Education & empowerment
- “not a life-threatening condition”, support groups, education links, etc
- 4) PFMT + biofeedback
- 4) Behaviour modification } helpful in the short-term, especially for frequency-predominant IC
- voiding diary + timed voiding + controlled fluid intake
- stress reduction + exercise
- 5) Massage (soft tissues)
- 6) Acupuncture
- 7) Dietary changes
- caffeine, EtOH, spicy foods, acidic drinks, cheese, citrus fruits, preservatives, etc

Table 10-10 -- Interstitial Cystitis Association Recommendations of Foods to Avoid

<i>Milk/Dairy Products</i>	<i>Nuts</i>
Aged cheeses	<i>Beverages</i>
Sour cream	Alcoholic beverages including beer and wine
Yogurt	Carbonated drinks
Chocolate	Coffee
<i>Vegetables</i>	Tea
Fava beans	Fruit juices
Lima beans	<i>Seasonings</i>
Onions	Mayonnaise
Tofu	Ketchup
Soybeans	Mustard
Tomatoes	Salsa
<i>Fruits</i>	Spicy foods: (Chinese, Mexican, Indian, Thai)
Apples	Soy sauce
Apricots	Miso
Avocados	Salad dressing
Bananas	Vinegar
Cantaloupes	<i>Preservatives and Additives</i>
Citrus fruits	Benzyl alcohol
Cranberries	Citric acid
Grapes	Monosodium glutamate
Nectarines	Artificial sweeteners
Peaches	Preservatives
Pineapples	Artificial ingredients
Plums	Food coloring
Pomegranates	<i>Miscellaneous</i>
Rhubarb	Tobacco
Strawberries	Caffeine
Juices from above fruits	Diet pills
<i>Carbohydrates and Grains</i>	Junk foods
Rye bread	Recreational drugs
Sourdough bread	Allergy medications with ephedrine or pseudoephedrine
<i>Meats and Fish</i>	Certain vitamins
Aged, canned, cured, processed, smoked meats and fish	

ORAL THERAPY

What are some of the oral therapies used for PBS/IC? }} “PATCH It ‘N GO”

- 1) **TCAs** → “PACH” proven in RCTs
 - Amitriptyline } **staple medication for IC**
 - } best results with higher bladder capacity (>450cc)
 - } 25 to 100mg po qHS (lower than dose for depression; 150-300)
 - } 40-50% response in RCTs
 - careful if on psych meds or if arrhythmia (QT)
- 2) anti-histamines
 - Hydroxyzine (Atarax) } H1-receptor blocker
 - } ~30% response in RCTs
 - Cimetidine } H2-receptor blocker
 - } ~60% response rate in RCTs
- 3) **Pentosan Polysulfate (PPS)** } synthetic heparin analogue (GAG)
ie ELMIRON } 100 to 300mg po TID (only 3-6% excreted in urine)
 - } ~30% response rate in RCTs
- 4) analgesics
 - NSAIDs, Opioids, anticonvulsants (**Gabapentin, Topiramate**)
- 5) Immunosuppressive
 - steroids, cyclosporine, MTX } some response but bad S/E profile with long-term use
- 6) others
 - **no benefit on RCT** } nalmefene (opiate antagonist), L-arginine (amino acid), benzydamine (antiinflammatory)
 - no RCTs } nifedipine, Quercetin (bioflavonoid), montelukast (anti-leukotriene)

What are the different mechanisms by which TCAs help with IC?

- 1) central and peripheral anticholinergic actions (at some sites)
- 2) blocks presynaptic reuptake of serotonin and noradrenaline
- 3) sedative
- 4) potent H1-histaminergic receptor blocker
- 5) stimulate β -adrenergic receptors in bladder smooth muscle

What are the contraindications to TCA therapy?

- **long QT syndrome**
- significant heart blocks
- recent MI (within 6/12)
- unstable angina
- CHF
- frequent PVCs
- hx of sustained ventricular arrhythmias
- orthostatic hypoTN
- severe liver disease
- closed-angle glaucoma

What are the side effects of TCAs?

- drowsiness/sedation
- nausea
- constipation
- dry mouth
- postural hypoTN
- decreased libido
- increased appetite and wt gain
- arrhythmias

What are the side effects of oral sodium Pentosan Polysulfate (Elmiron)?

- alopecia (reversible)
- diarrhea
- nausea
- skin rash
- headache
- dizziness
- abdo pain
- bleeding problems (rare)
- may promote breast CA in those at high-risk

INTRAVESICAL AND INTRADETRUSOR THERAPY

What are some of the intravesical therapies used for PBS/IC? }} “Little SHePherD B”

→ “PD” proven in RCTs

- 1) Lidocaine mix
- 2) Pentosan polysulfate (PPS) } GAG analogue
 - } 300mg in 50cc NS
 - } 40% response rate on RCT
- 3) Dimethyl sulfoxide (DMSO) } derivative of lignin (product of wood pulp industry)
 - ie RIMSO } 50cc of 50% DMSO
 - } ↓d mast cell histamine release & desensitizes nociceptive pathways
 - } 70% response rate on RCT
 - } no side effects except garlic-breath
- 2) Silver nitrate } oldest treatment
 - } 50-70% response rates
 - } contraindicated in VUR, recent bladder surgery
- 3) Heparin } GAG analogue + anti-inflammatory effects
 - only GAG not normally found in bladder
 - } 10K-40K units instilled
 - no systemic absorption
 - } adding lidocaine and/or DMSO may improve outcomes
 - } ~60% response rates
- 5) intradetrusor Botulinum toxin A } currently being researched
- 6) others
 - **no benefit on RCT** } resiniferatoxin (capsaicin analogue), hyaluronic acid (GAG), BCG
 - no RCTs } Clorpactin WCS-90, chondroitin sulfate, oxybutynin

NEUROMODULATION

What are some of the neural-based treatments that have been used for PBS/IC?

- 1) TENS (transcutaneous electrical nerve stimulation)
 - relief of pain by stimulating myelinated afferents to activate segmental inhibitory circuits
 - may also reduce urinary frequency
 - high or low frequency (2-50 Hz)
- 2) acupuncture
 - treatment at Sp. 6 point
- 3) lumbar epidural blockade
- 4) neuromodulation
 - direct sacral nerve stimulation (most commonly S3)
 - best results for those with pain + pelvic muscle dysfunction
 - trial stimulation period before implanting permanent neural prosthesis
 - also used for refractory urge incontinence

HYDRODISTENSION

What is the role of hydrodistension?

- **efficacy related to damage to mucosal afferent nerve endings**
- better results if done under GA
- no standard method of distension
 - 80cm of H₂O
 - can also look for glomerulations and Hunner's ulcers
 - prolonged distension likely has no benefit over short-term distension (minutes)
- must always consider risk of perforation or rupture
- hematuria, low back pain common
 - worsening of symptoms can occur in ~5%
- **not effective Rx BUT may give prognostic information**
 - capacity <200cc under GA (rare) predicts failure of medical therapy more likely

SURGICAL THERAPY

What are some of the surgical therapies used for PBS/IC?

- **option only AFTER ALL TRIALS OF NON-SURGICAL RX HAVE FAILED**
- “primum non nocere”
- 1) transurethral resection of Hunner's ulcers
 - provides symptomatic relief
- 2) supratrigonal cystectomy + augmentation
 - mixed results
 - may need CIC post-op } disaster for IC patients
- 3) total cystectomy + conduit or neobladder
 - recommended if trigone “affected” by IC
- 4) diversion
 - may be complicated by pyocystitis, hemorrhage, severe pain, and unremitting spasms and feelings of incomplete emptying
- 5) historical approaches
 - sympathectomy
 - intraspinal alcohol injections

List therapeutic options for refractory IC/PBS.

- “THE NARC”
- TENS
- Hydrodistension
- Epidural blocks (lumbar)
- Neurostim device
- Acupuncture
- Resection of Hunner's ulcers
- Cystectomy

PRINCIPLES OF MANAGEMENT

What is the diagnosis and treatment algorithm for possible PBS/IC?

- 1) Initial assessment
 - History
 - bladder pain with urinary frequency & nocturia +/- urgency, relieved by voiding
 - age >18yrs, duration >6months, incontinence
 - voiding diary, fluid intake, caffeine intake, bowel habits, sexual hx
 - associated symptoms } CVA tenderness, N/V, fever, chills, wt loss, night sweats
 - PMHx } stones, UTIs, STDs, GU cancers, chemo (cyclophosphamide), hx of GU TB, RADs, neurogenic bladder (MS, SCI, stroke), urethral strictures, depression, anxiety
 - associated diseases (“ASS IF Vestibulitis”)
 - Meds, allergies, smoker, EtOH, drugs, occupational exposure
 - IC/PBS questionnaires } U of Wisconsin IC scale, O’Leary-Sant symptom index, PUF symptom scale
 - Physical Exam
 - general appearance, vitals
 - abdo exam } masses
 - genital exam } ulcers, diverticulum, tumours
 - bimanual in women
 - neurologic } focused exam
 - lab tests
 - urinalysis, urine C&S, urine cytology
 - for research purposes } urine for APF/mastcells/GAG
 - +/- imaging (if indicated)
 - U/S
 - CT abdo/pelvis
 - +/- cystoscopy (if indicated)
 - mainly to r/o other etiologies
 - pain on bladder filling with reproduction of symptoms suggestive of IC
- 2) Initial management
 - conservative therapy (“AWE, Poor Bladder’s MAD”)
 - consider empirical course of ABx (if ABx naïve)
 - patient education and empowerment
 - behaviour modification (pelvic floor relaxation, etc)
 - dietary changes
 - nonprescription analgesics
 - oral and intravesical therapy
 - amitriptyline, pentosan polysulfate, cimetidine, etc } “PATCH It ‘N GO”
 - DMSO, pentosan polysulfate, lidocaine, heparin, etc } “Little SHPD B”
- 3) Secondary assessment
 - failure of initial Rx warrants further evaluation
 - UDS, pelvic imaging, cystoscopy + hydrodistension +/- Bx
 - hydrodistension alone therapeutic in 30% (usually short-term only)
 - trial of anti-cholinergics if evidence of bladder overactivity
 - TUR or fulguration with evidence of Hunner’s ulcer
- 4) Refractory PBS/IC
 - failure of oral, intravesical therapy and minimally invasive surgical options (hydrodistension, TUR, fulguration, etc) warrants more aggressive modalities
 - neuromodulation, pain clinic, narcotic analgesics
 - experimental protocols
 - LAST RESORT ONLY
 - surgical therapy (augmentation cystoplasty, urinary diversion +/- cystectomy)

URETHRAL SYNDROME

What is urethral syndrome?

- nonspecific constellation of symptoms including frequency, urgency, dysuria, and suprapubic discomfort WITH NO OBJECTIVE UROLOGIC ABNORMALITIES
- acute vs chronic

➔ **HISTORICAL DIAGNOSIS**

Table 10-13 -- Causes of Frequency and Urgency

Interstitial cystitis
Upper motor neuron lesion
Habit
Large fluid intake
Pregnancy
Bladder calculus
Urethral caruncle
Radiation cystitis
Large postvoid residual
Genital condylomata
Diabetes mellitus
Cervicitis
Periurethral gland infection
Atrophic urethral changes
Urinary tract infection
Chemical irritants: contraceptive foams, douches, diaphragm, obsessive washing
Overactive bladder
Vulvar carcinoma
Diuretic therapy
Bladder cancer
Urethral diverticulum
Pelvic mass
Chemotherapy
Bacterial urethritis
Renal impairment
Diabetes insipidus

Chapter #11 – STDs

EPIDEMIOLOGY AND TRENDS

How common are STDs?

- 15 million new cases reported each yr
- 65 million people have incurable viral STDs
- 2/3 of cases occur in adolescents & young adults
- 5 of the top 10 notifiable infectious diseases in the US were STDs
 - doesn't include HPV and HSV (not reportable)

What is the most common STD?

- **HPV and HSV**
 - by age 50, >80% of women will have genital HPV
 - not reportable STDs
- *Chlamydia* is the most common bacterial STD

Which STDs are on the decline?

- chancroid → most cases from S. Carolina area
- gonorrhea (slight decrease only) → increasing quinolone resistance esp Hawaii & California
 - quinolones NOT recommended for Rx of gonorrhea in these states

Which STDs are on the rise?

- HPV
- *Chlamydia* → 2x more common than gonorrhea

Which STDs have remained stable?

- primary and secondary syphilis → increasing in men but decreasing in women
 - could be due to gay sex
- high rates among blacks

What are the potential consequences of STDs in women?

- PID
- ectopic pregnancy
- infertility
- pain
- perinatal infections

Which STDs require the MD to trace contacts and treat sexual partners?

- syphilis
- gonorrhea
- chlamydia

GENITAL ULCERS

What are the CDC recommendations for the work-up of a genital ulcer?

- co-infections are not uncommon } 10% with chancroid also have HSV or syphilis
- 1) **serology + darkfield exam or direct immunofluorescence for *T. pallidum* (syphilis)**
 - 2) **viral culture or antigen test for HSV**
 - 3) **culture for *H. ducreyi* (chancroid)**
 - 4) start empiric treatment for most likely cause (based on Hx and P/E) while labs are pending
 - 5) if ulcers don't respond to Rx or appear unusual, Bx the ulcer
 - 6) consider HIV testing if +ve for STD

What are the 4 sexually transmitted genital ulcers (STD)?

	1° Syphilis	Chancroid	Herpes	Lymphogranuloma venereum
organism	<i>Treponema pallidum</i>	<i>Haemophilus ducreyi</i>	HSV type 2	<i>Chlamydia trachomatis</i>
lesion	single chancre	usually multiple ulcers	multiple vesicles or ulcers	single vesicle that progresses to ulcer
Local Symptoms	painless	PAINFUL & PURULENT	PAINFUL	painless
LN status	painless BILATERAL	PAINFUL & SUPPURATIVE UNILATERAL	PAINFUL BILATERAL	PAINFUL & SUPPURATIVE UNILATERAL
Systemic Symptoms	none	none	+++ during primary infection	+++ after lesion heals
1 st line Rx	Pen G (Doxycycline if allergy)	Azithromycin (Ceftriazone, cipro)	Acyclovir (Famciclovir)	Doxycycline (Erythromycin)

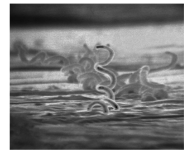
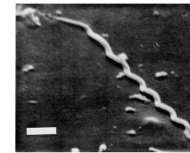
→

	S	C	H	L
lesion	single	bilateral	bilateral	single
symptoms	painless	painful	painful	painless
nodal symptoms	painless	painful	painful	painful
nodes	bilateral	unilateral	bilateral	unilateral

What are some non-sexually transmitted causes of genital ulcers?

- "Big FAT CLERC"
- Behcet's syndrome
 - Fixed drug reaction
 - Amebiasis
 - Trauma
 - Crohn's disease
 - Lichen planus
 - Erythema multiforme
 - Reiter's syndrome (reactive arthritis)
 - Carcinoma

Syphilis



Hideyo Noguchi - Japanese bacteriologist who first discovered *Treponema pallidum*, the causative agent of syphilis, in the brains of persons suffering from paresis.

SYPHILIS

What is the cause of syphilis?

- **spirochete *Treponema pallidum***
- incubation period ranges from 10-90 days
- can be acquired through sexual intercourse, in utero & through blood transfusions

How does primary syphilis present?

- **PAINLESS** genital ulcer/CHANCRES } **SINGLE lesion** \
- **PAINLESS, BILATERAL inguinal LNs** } often goes unnoticed
- no systemic symptoms /

What is the natural hx of syphilis?

- **primary syphilis** } ulcer/chancere appears at site of inoculation ~3 weeks after inoculation
 - ulcer persists for 4-6 weeks
- **latent syphilis stage** } +ve seroreactivity BUT no clinical evidence of disease
- **secondary syphilis** } presents anywhere from 1 month to 2yrs after appearance of ulcer
 - } mucocutaneous, constitutional, and parenchymal findings
 - maculopapular rash (trunks and arms)
 - generalized nontender lymphadenopathy
 - papular lesions on palms/soles that become necrotic & pustular
 - may develop large papules in inter-triginous areas that erode to produce condyloma lata (very infectious)
 - may develop hepatitis, immune-complex GN
- **tertiary syphilis** } develops in 1/3 of untreated patients (rare in developed world)
 - } systemic disease that especially affects CVS, skeletal system, CNS, & skin
 - aortitis
 - meningitis
 - optic neuritis
 - skin and skeletal gummas
 - tabes dorsalis
 - uveitis
 - general paresis

How do you make the Dx of syphilis?

- 1) **non-treponemal serology** } ~85% sensitivity for primary syphilis but sensitivity is 100% for secondary syphilis and >95% for tertiary syphilis
 - (RPR or VDRL)
 - } antibody titers correlate with disease activity
 - becomes -ve 1yr after treatment
 - } **all +ve tests should be confirmed with treponemal testing**
 - T. Pallidum particle agglutination (TP-PA)
 - fluorescent treponemal Ab absorbed test (FTA-ABS)
- 2) direct immunofluorescence } readily available
- 3) **darkfield microscopy** } not widely available

Which patient populations are at increased risk for syphilis?

- pregnant women
- gay men
- high-risk sexual behaviour
- working in adult jails

Syphilis

- Bacterium *Treponema pallidum*
 - spirochete
- Incubation period → 3 weeks (10-90 days)
- **Ulcer**
 - Single, painless, **firm** ulcer
 - Persists for 4-6 weeks
 - Often goes unnoticed



Syphilis



Syphilis

- Manifestations of primary syphilis:
 - A) **hard chancre (lesion on female)**
 - Syphilitic chancres are indurated
 - They are highly infectious
 - Often on glans, corona or perineal area on men.
 - They may occur **anywhere** on the body
 - They are **painless**
 - B) **regional lymphadenitis**
 - Regional lymphadenopathy adjacent to the chancre may develop during primary syphilis.
 - The nodes are firm, nonsuppurative
 - It may persist for months, despite healing of the chancre.

Syphilis

- **Latent**
 - Defined as sero-reactivity
 - No clinical evidence of disease
- **Secondary**
 - Begins 4-10 weeks after initial ulcer
 - **Manifestations:**
 - Mucocutaneous
 - Maculopapular rash (trunk & arms)
 - Progress to papular rash (palm & soles)
 - » endarteritis
 - Condyloma lata
 - Constitutional
 - Generalized, nontender lymphadenopathy

Syphilis

- **Secondary**
 - Maculopapular rash
 - Trunk & arms



Syphilis

- **Secondary**
 - Papular rash
 - Palms and soles

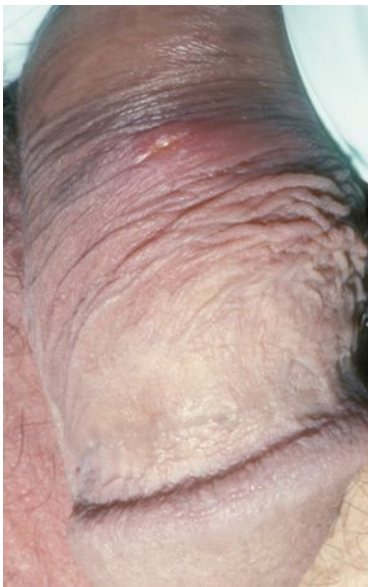


What is the treatment of syphilis?

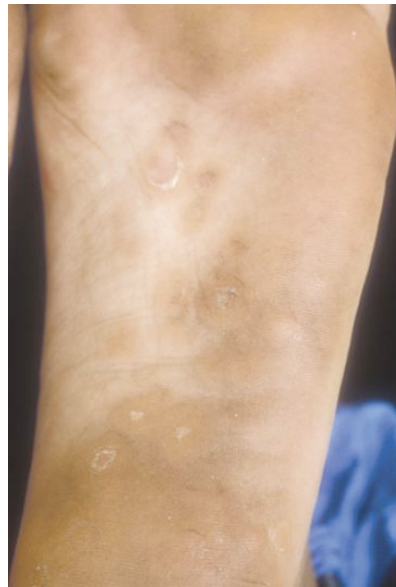
- primary syphilis
 - 1) **Pen G 2.4 million units IM x 1 dose**
 - 2) **if pen allergic, doxycycline 100mg po bid x 14days**
- latent syphilis or secondary syphilis
 - 1) Pen G 2.4 million units IM q1week x 3 doses
 - 2) if pen allergic, doxycycline 100mg po bid x 4wks
- tertiary syphilis
 - 1) **aqueous crystalline Pen G 3-4 million units IV q4h x 10-14days**
 - 2) Pen G procaine 2.4 million units IM od + probenecid 500mg po qid x 10-14days
- follow patients with nontreponemal Ab titers (RPR or VDRL) at 6 and 12 months
 - follow more frequently if HIV +ve
 - 4-fold decrease in titers = cure
 - if treatment fails, re-treat and check CSF to r/o neurosyphilis

What is the Jarish-Herxheimer reaction?

- **reaction to Pen G that occurs within first 24hrs after Rx for syphilis**
 - H/A + myalgia + fever + tachycardia + tachypnea
- Rx → bedrest + NSAIDs
- watch for fetal distress in infants or preterm labour in pregnant women



→ PRIMARY SYPHILIC CHANCER/ULCER



→ SECONDARY SYPHILIS



→ PRIMARY SYPHILIS



HERPES SIMPLEX VIRUS INFECTION

What is the cause of genital herpes?

- 85-90% from **HSV-2**
- 10-15% from HSV-1 } exposure to HSV-1 as child decreases future risk of HSV-2 infections
- incubation period is ~4 days (ranges from 1-26 days)

How does genital herpes present?

- **silent infection in ~75%** } 80% of women +ve for HSV-2 Abs have no hx of clinical herpes
- atypical presentations } abrasions, fissures, itching
→ more common in women
- classic presentation not common
→ **PAINFUL** genital or anal **ULCERS** or groups of **VESICLES on erythematous base**
- usually **MULTIPLE**
- **PAINFUL, BILATERAL inguinal LNs**
- **+++ flu-like symptoms DURING primary infection**

What is the natural hx of genital herpes?

- recurrent outbreaks usually less severe and only involve ulcers
→ recurrences much more common with HSV-2
→ rare to see recurrence of HSV-1 after 1st year
- asymptomatic viral shedding can occur for 3 months, perpetuating risk of transmission

What are the potential complications of herpes infections?

- pneumonitis
- disseminated infection
- hepatitis
- meningitis
- encephalitis

How do you make the Dx of genital herpes?

- 1) **viral culture & subtyping** } cheap, very specific, and results in 5days
→ **current GOLD STANDARD**
} poor sensitivity
→ viral load highest when lesion is vesicular and during primary infection
} essential to know viral subtype
- 2) **viral antibody assay** } identify antibodies to HSV glycoproteins G-1 and G-2
→ gives info on subtype
} may also be able to identify whether primary infection or recurrence
→ based on antibody avidity
- 3) **viral antigen PCR testing** } more sensitive than viral culture with more stable samples
} can't identify subtype
} no yet approved but coming → may replace viral culture
- 4) **Tzanck smear** } stain for inclusion bodies

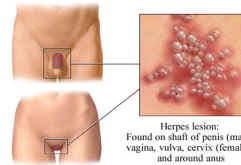
HSV

- Common (10% of US population)
- Afflicting >50 million/year in USA
- Caused by HSV-2 in 85-90%
- Silent infection is common
- 75% of viral transmission
- Incubation → 4 days (1-26 days)



• Primary manifestation:

- Painful ulcer
- Bilateral painful inguinal adenopathy (75%)
- "group of vesicles on an erythematous base that does not follow a neural distribution" is pathognomonic



HSV



- **In females** → labia majora and minora, vaginal mucosa, cervix, and perineal region.
- **In males** → glans penis, the prepuce, and the shaft of the penis.



HSV

- Lesions are self-limiting
• heal in ~ 3 weeks
- May also be associated with:
 - Atypical lesions (abrasions, fissures, itching)
 - Constitutional symptoms
 - Headache
 - Malaise
 - Myalgias
 - 15% also have herpetic pharyngitis
 - Sacral radiculopathy
 - Urinary retention
- Asymptomatic viral shedding can take place for up to 3 months following clinical presentation

HSV

-Initial manifestations include:
local pain, tenderness, itching sensation, dysuria, and in females, a profuse, watery vaginal discharge.

-Initial lesions
papules on a red erythematous base but they rapidly develop into vesicles and later ulcers covered with a grayish exudate.



HSV Summary

- **Herpes**
 - Hurts
 - Vesicles
 - Multiple
 - Erythematous base
 - Adenopathy
 - Bilateral
 - Culture
 - Antiviral therapy
 - No cure

What is the treatment of genital herpes?

→ oral therapy } topical anti-viral meds NOT EFFECTIVE

A) primary infection

- 1) **acyclovir } 400mg tid x 7-10days**
- 2) **famciclovir } 250mg bid x 7-10days**
- 3) valacyclovir } 1g bid x 7-10days

B) recurrences

→ suppressive Rx

- 1) **acyclovir } 400mg bid**
- 2) **famciclovir } 250mg bid**
- 3) valacyclovir } 500mg od
 } 1g od

→ episodic Rx

- 1) **acyclovir } 400mg tid x 5days**
- 2) **famciclovir } 125mg bid x 5days**
- 3) valacyclovir } 500mg bid x 5days
 } 1g od x 5days

What is the role of daily suppressive Rx for genital herpes?

→ safe & effective

- prevents ~80% of recurrences
- decreases frequency & duration of recurrences
- decreases viral shedding



→ GENITAL HERPES ULCERS



→ GENITAL HERPES VESICLES

LYMPHOGRANULOMA VENEREUM

What is the cause of lymphogranuloma venereum?

- ***Chlamydia trachomatis*** } **types L1, L2, and L3**
- extremely rare in US
- incubation period ranges from 3-30 days

How does lymphogranuloma venereum present?

- **PAINLESS genital ulcer** } **SINGLE lesion**
 - } starts out as vesicle that progresses to ulcer
 - } can involve penis, anus, or vulvovaginal area
- **PAINFUL, UNILATERAL inguinal LNs** } suppurative and tend to fistulize
- **+++ constitutional symptoms** } occurs 2-6 weeks AFTER resolution of ulcer

What are the potential complications of lymphogranuloma venereum?

- labial fenestration
- urethral destruction
- scrotal/labial fusion
- anorectal fistulae
- elephantiasis of the penis, scrotum, or labia

How do you make the Dx of lymphogranuloma venereum?

- 1) **mainly clinical diagnosis**
- 2) culture } only +ve in 30-50%
- 3) **complement fixation titer** } titer >64 confirms Dx
- 4) indirect fluorescence antibody titers } used to confirm Dx

What is the treatment of lymphogranuloma venereum?

- 1) **doxycycline 100mg po bid x 3 weeks**
- 2) **erythromycin 500mg po qid x 3 weeks**



→ LYMPHOGRANULOMA VENEREUM

CHLAMYDIA TRACHOMATIS INFECTION

How common is Chlamydia?

- **most common bacterial STD** } virulent serotypes include D, E, F, G, H, I, J, and K

How is Chlamydia transmitted?

- ***Chlamydia trachomatis* (gram-negative)** } incubation period ranges from 3 to 14 days
- congenital } newborn infection during vaginal birth (exposure of mom's infected cervix)
- sexual transmission } squamous cells of vaginal epithelium are relatively resistant to infection but columnar cells of cervix are not resistant

How does Chlamydia present?

- sexual transmission
 - **50% of men have symptoms** attributed to urethritis, epididymitis, or prostatitis
 - may have clear or white urethral discharge
 - most common cause of epididymitis in young men
 - **75% of women are asymptomatic**
 - may have mucopurulent endocervical discharge
 - 40% with untreated infection will develop PID
- congenital infection
 - ocular, oropharyngeal, respiratory, urogenital, or rectal infections

How do you Dx Chlamydia?

- 1) **nucleic acid amplification test (NAAT) of endocervical/intraurethral swab**
 - most sensitive
 - gives Abx sensitivities
 - if used to assess cure, don't test <3 weeks after finishing Rx (can get false +ve)
 - 2) **NAAT of urine**
 - sensitive and noninvasive (doesn't need pelvic exam)
 - can't give Abx sensitivity
 - 3) unamplified nucleic acid hybridization test or enzyme immunoassay or direct fluorescent antibody titer of endocervical/intraurethral swab
 - 4) culture of endocervical/intraurethral swab
 - difficult to culture
- screening recommended annually in women until age 25 or if +ve RFs (new sexual partner)
 - in men, intraurethral samples used for testing

What is the treatment for Chlamydia?

- 1) **azithromycin 1g po x 1 dose** \ no need to test for cure
 - 2) **doxycycline 100mg po bid x 7days** } no sex for 7 days
 - 3) ofloxacin 300mg po bid x 7days /
 - 4) erythromycin base 500mg qid x 7days } lower cure rate → need to test for cure 3wks later
- **high risk of reinfection** } **all patients should be re-screened 3-4 months after Rx**
 - all sexual partners within 60days should be tested and treated } for gonorrhea and chlamydia

GONORRHEA

How is gonorrhea transmitted?

- not as common as Chlamydia
- ***Neisseria gonorrhoeae* (GN diplococcus)** } incubation period ranges from 3 to 14 days
- sexual transmission } risk after one exposure 4x higher in women (10% vs 40%)
 - squamous cells of vaginal are relatively resistant to infection but columnar cells of Cx are NOT

How does gonorrhea present?

- **most M have LUTS** attributed to urethritis, epididymitis, proctitis or prostatitis
 - mucopurulent urethral discharge
- **most F are asymptomatic**
 - women may have vaginal or pelvic discomfort or dysuria \ can lead to PID, regardless
 - mucopurulent endocervical discharge may be present / of symptoms

What are the manifestations of disseminated gonococcal infection?

- rare today } arthritis, meningitis, endocarditis, dermatitis

How do you Dx gonorrhea?

- 1) **culture of endocervical/intraurethral swab** } CDC recommendation for screening
- 2) **NAAT of endocervical/intraurethral swab**
- 3) nucleic acid hybridization test of endocervical/intraurethral swab
- 4) NAAT of urine } if endocervical/intraurethral specimen not available (less sensitive)
- screening recommended annually in women until age 25 or if +ve RFs (new sexual partner)

What is the treatment for gonorrhea?

- 1) **ceftriaxone 125mg IM x 1 dose**
- 2) **cefixime 400mg po x 1 dose**
- 3) **cipro 500mg po x 1 dose** \
- 4) levofloxacin 250mg po x 1 dose } high quinolone resistance in Asia, the Pacific,
- 5) ofloxacin 400mg po x 1 dose / Hawaii, and California
- coinfection with *C. trachomatis* common } **Rx for Chlamydia for all with +ve gonorrhea**
 - Azithro 1g po } cheaper than to test for Chlamydia
- all sexual partners within 60days should be tested & treated } for gonorrhea & chlamydia

What is the etiology of non-gonococcal urethritis?

- urethritis in gay men more likely to be gonococcal
- 1) *Chlamydia trachomatis*
- 2) *Ureaplasma urealyticum*
- 3) unknown } *Mycoplasma genitalium* & *Trichomonas vaginalis* have been implicated

Differentiate gonococcal from non-gonococcal urethritis

Feature	GU	NGU
Organism	N. gonorrhea	C. trachomatis
Type	GN diplococci	Intracell facultative anaerobe
Incubation	3 – 10 days	1 – 5 wks
Urethral d/c	Profuse, purulent	Scant
Asymptomatic carriers	40 – 60%	40 – 60%
Dx	Ligand chain rxn	Ligand/PCR
Abx	Ceftriaxone, cefixime, cipro	Azithro, doxy, erythro

TRICHOMONIASIS

Table 11-3 -- Differential Diagnosis of STDs in Women

	Vaginal Discharge	pH	WBC	Microscopy	Symptoms
Normal	White, thick, smooth	≤4.5	Absent	Lactobacilli	None
Candidiasis	White, thick, curdy	≤4.5	Absent	Mycelia	Vulvar pruritus, external or superficial dysuria
Trichomoniasis	Frothy or purulent	≥4.5	Present	Mobile trichomonads present	Vulvar erythema and edema, punctate strawberry lesions on cervix
				Amine odor	
<i>Neisseria gonorrhoeae</i>	None or mucopurulent discharge from cervicitis	≥4.5	Present	Gram-negative diplococci within or adjacent to polymorphonuclear leukocytes on Gram stain	Vaginal and pelvic discomfort, dysuria, most often asymptomatic
<i>Chlamydia trachomatis</i>	None or mucopurulent discharge from cervicitis	≥4.5	Present	Organisms not visualized	Vaginal and pelvic discomfort, dysuria, most often asymptomatic
Bacterial Vaginosis	Thin, white homogeneous	≥4.5	Absent	Paucity of lactobacilli (75% of patients)	Fishy odor and increased vaginal discharge
				Amine odor	
				Clue cells	

How common is trichomoniasis?

- very common STD } ↑'ing incidence in developing countries and in promiscuous women

How is trichomoniasis transmitted?

- ***Trichomonas vaginalis* (flagellated protozoan)** } incubation period ranges from 4 to 28 days
- sexual transmission } can inhabit vagina, urethra, Bartholin glands, Skene's glands, prostate
- } does NOT infect rectum or mouth

How does trichomoniasis present?

- **usually asymptomatic in men**
 - may have short-lived LUTS and urethral discharge
- **50% of women are asymptomatic**
 - frothy white or green, **foul-smelling vaginal discharge (basic pH)**
 - **“strawberry vulva” or “strawberry cervix”**
 - pruritus and erythema, dyspareunia, S/P discomfort, LUTS
 - can induce premature labour
- associated with ↑'d risk of HIV transmission

How do you Dx trichomoniasis?

- characteristic **“strawberry vulva or cervix”**
- alkaline pH vaginal discharge
- **motile protozoa seen on vaginal wet-mount smear or urine microscopy**
- in males, urethral swab culture or urine microscopy
- NAAT, immunofluorescence, standard culture techniques also available

What is the treatment for trichomoniasis?

- 1) **flagyl 2g po x 1 dose**
 - flagyl 500mg po bid x 7 days for failures
 - repeat testing at 5-7 days and 30 days if symptoms persist or failure suspected
 - intravaginal Rx not as effective

GENITAL WARTS

What is the cause of genital warts?

- aka condylomata acuminata
- **HPV** } DNA virus spread by skin-to-skin contact
 - over 100 types exist } >30 types can infect the genital area
 - } **most infections are subclinical & asymptomatic**
 - median duration of infection = 8 months
 - only ~10% remain infected after 2 yrs
 - } long, variable incubation period
- external warts typically caused by **HPV types 6 & 11** } can be infected with >1 type
 - } inoculation occurs at site of genital trauma

Which types of HPV are associated with an increased risk of carcinoma?

- penile, cervical, anal, vulvar, vaginal carcinomas
 - ~100% of cervical cancer and >80% of anal cancers are associated with HPV
- types 6, 11, **16, 18**, 31, 33, 35, 39, 45, 51

What are the RFs for acquiring HPV infection?

- multiple sexual partners
- early age at onset of sexual intercourse
- sexual partner with HPV

How is HPV transmitted?

- direct skin-to-skin contact

How do HPV infections present?

- women } nonspecific symptoms (vulvodynia, pruritus), malodorous vaginal discharge, genital warts
 - } subclinical infections
 - most F partners of M with HPV warts have HPV infection
 - } high rate of coinfection with other STDs
- men } genital warts, intraurethral warts, bladder lesions
 - } subclinical infections
 - found in 50-75% of steady M partners of F with HPV

How do you Dx genital warts?

- 1) visualization or palpation of **nontender papillomatous genital lesions**
- 2) **aceto-whitening with 3-5% acetic acid** } may show subclinical, flat condylomata
 - routine evaluation of asymptomatic M partners of women with HPV infection NOT RECOMMENDED
 - Bx only recommended if atypical warts } pigmented, indurated, ulcerated, fixed
 - } persistent or worsening after Rx
 - see **kilocytes** with HPV infection (condyloma acuminata)

What is the treatment for genital warts?

- HPV infection & recurrence is common among sexually active people
- depends on wart size, number, and location as well as patient/physician preference
- 1) **observation** } genital warts spontaneously resolve with time
- 2) **patient-applied Rx** (contraindicated in pregnancy)
 - a) podofilox 0.5% solution or gel q12hrs (Max 0.5 mL/day) x 3days
 - b) imiquimod 5% cream 3x per wk x ≤16 wks } don't use on vagina (can cause chronic ulcers)
- 3) **provider-applied Rx**
 - a) liquid nitrogen
 - b) electrosurgery
 - c) laser therapy
 - d) surgical excision
 - e) podophyllin resin 10-25% (contraindicated in pregnancy)
 - apply once weekly, washed off 1-4 hrs after Rx
 - f) trichloroacetic acid 80-90% (NOT for large or keratinized warts)
 - apply once q1-2 wks
 - g) intraurethral 5% 5-FU cream twice weekly
- all women with genital warts should get gyne evaluation } vagina & cervix
- large lesions surrounding meatus may indicate urethral or bladder lesions
 - cysto is recommended } avoid traversing EUS if distal lesion (don't contaminate bladder)

MOLLUSCUM CONTAGIOSUM

What is molluscum contagiosum?

- **double-stranded DNA virus from the Poxviridae family**
- 4 known subtypes } doesn't influence disease presentation or course
 - } MCV-1 most common in US
 - } MCV-2 most common in Europe, Australia, HIV patients
- incubation period ranges from 14-50 days

How is molluscum contagiosum transmitted?

- skin-to-skin contact
- fomites
- self-inoculation

How does molluscum contagiosum present?

- **smooth, round, pearly papules**
- lesions are usually small (2-5mm)
 - large lesions (>5mm) are more common in immunocompromised patients
- **subtle central umbilication** } **can resemble herpes vesicle but these are NOT painful**
- erythematous or hypopigmented halo at base
- usually asymptomatic but can get itchy
- kids } cluster of lesions on face, neck, chest, back & extremities
- adults } genital & inguinal regions, inner thighs & perineum

How do you Dx molluscum contagiosum?

- **clinical suspicion** } confirmed with H&E staining of Bx specimen
 - presence of **acidophilic, hyaline-filled Henderson-Patterson bodies**

What is the treatment for molluscum contagiosum?

- 1) **observation for most** } in immuno-COMPETENT pts, usually resolves w/in a few months to 1yr
 - 2) cautery
 - 3) curettage
 - 4) liquid nitrogen
 - 5) imiquimod cream (1% or 5%) tid } good option for HIV patients
- **should test for other STDs, condyloma acuminata, and pubic lice**
→ also consider HIV testing if extensive multi-site lesions (esp. involving head and neck)



→ GENITAL MOLLUSCUM CONTAGIOSUM



→ MOLLUSCUM CONTAGIOSUM

OVERVIEW OF OTHER SEXUALLY ASSOCIATED INFECTIONS

Mollicutes

What is the significance of mollicutes?

- *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Mycoplasma genitalium*
→ commensal organisms of GU tract in men and women
- implicated in chronic prostatitis in men, urgency/frequency syndromes in women, and up to 40% of nongonococcal urethritis cases
→ consider culturing for *Ureaplasma* and *Mycoplasma* for recurrent UTI-like symptoms
→ needs special agar to culture

What is the treatment for mollicutes?

- 1) **doxycycline 100mg po bid x 2wks**
 - 2) **azithromycin 1g po x 1 dose**
 - 3) tetracycline } 30% resistance
 - 4) erythromycin 500mg po qid x 10-14 days
 - 5) ofloxacin 300mg po bid x 10-14 days
- \ similar to regime for
/ Chlamydia

Bacterial Vaginosis

What is the cause of bacterial vaginosis?

- overgrowth of ***Gardnerella vaginalis* (anaerobic organism) and *Mycoplasma hominis***
- inhibition of N vaginal flora } particularly *Lactobacillus*

What is the clinical significance of bacterial vaginosis?

- increased risk of HIV infection
- increased complications in pregnancy
- may lead to PID

How does bacterial vaginosis present?

- non-specific low-grade genital discomfort
- malodorous vaginal discharge (especially after sex)

What are the RFs for bacterial vaginosis?

- increased number of sexual partners
- douching
- abN uterine bleeding
- contraceptive use

How do you Dx bacterial vaginosis?

→ **requires 3 of 4 factors to make the Dx**

- 1) **thin, white vaginal discharge that covers vagina**
- 2) **vaginal pH >4.5**
- 3) **+ve 10% KOH whiff test** } **fishy odor** suggests bacterial vaginosis
→ from release of amines
- 4) **microscopy** } **clue cells** (WBCs with bacteria attached to cell membrane)

What is the treatment for bacterial vaginosis?

- 1) **flagyl 500mg po bid x 7 days**
- 2) **clindamycin cream 2% intravaginally qHS x 7 days**
→ avoid douching

Vulvovaginal Candidiasis

What are the RFs for active vaginal candidiasis?

- hormonal changes resulting from pregnancy or contraception
- ABx use
- systemic corticosteroids
- anti-metabolites

What constitutes a “complicated” vulvovaginal candidiasis?

- recurrent
- non-*Candida albicans*
- infection during pregnancy
- severe
- infection in immunocompromised

How does vulvovaginal candidiasis present?

- **thick, cheesy vaginal discharge**
- vulvar irritation and itching
- dyspareunia
- dysuria

How do you Dx vulvovaginal candidiasis?

- vaginal discharge **10% KOH wet mount** } **shows yeast or pseudohyphae**
- **normal vaginal pH (<4.5)**

What is the treatment for vulvovaginal candidiasis?

- uncomplicated infections
 - 1) antifungal vaginal creams, tablets, or suppositories in “azole” class
 - 1 to 7 days depending on agent
 - eg clotrimazole, butoconazole, miconazole, terconazole
 - 2) po fluconazole 150mg po x 1 dose
- complicated infections
 - exclude DM, HIV, etc
 - consider maintenance therapy
 - 1) antifungal vaginal creams, tablets, suppositories (14 day regime)
 - 2) po fluconazole 150mg po x 1 dose, then repeat in 3 days x 1 dose

Granuloma inguinale

What is the etiologic agent in granuloma inguinale?

- **Calymmatobacterium granulomatis**
 - intracellular **GN bacillus related to *Klebsiella pneumoniae***
 - found in vacuolated inclusions in WBC called **Donovan bodies**
- uncommon in US, common in developing nations

Describe the physical findings in granuloma inguinale.

- incubation period 1-12 weeks
- small papule seen first, forms nodules
 - **nontender**, indurated, and firm
- **break down into beefy red ulcers**: base of ulcer erythematous, may bleed } sort of like pyoderma gangrenosum but more beefy red & cleaner
- **lymphadenopathy rare** in the absence of superinfection

How can one diagnose granuloma inguinale?

- **biopsy** of edge of ulcer, + identification of Donovan bodies on a stained smear
 - crush specimen for histologic study } Giemsa and silver stains
- **no culture available**

What is the treatment for granuloma inguinale?

→ Primary tx

- **Septra DS** 1 tab PO BID x 3 weeks
- **doxycycline** 100mg PO BID x 3 weeks

→ Alternatives

- cipro 750mg PO BID x 3 weeks
- erythromycin 500mg PO QID x 3 weeks
- azithromycin 1g PO q7d x 3 weeks



→ GRANULOMA INGUINALE

Chapter #12 – AIDS and HIV

EPIDEMIOLOGY

What is the epidemiology of AIDS/HIV around the world?

- developing world } mainly heterosexually transmitted
 - high mortality rates
 - majority of HIV/AIDS burden in the world is in Africa (2/3)
- industrialized world } disease of underprivileged & marginalized
 - mortality rates declining rapidly

What are the 3 main modes of HIV transmission?

- 1) unprotected sex } most common mode
- 2) contact with blood } most efficient transmission
- 3) mother to child

Table 12-2 -- HIV Infection Risk Associated with Sexual Behaviors Compared with Blood Exposure

Route/Type of Exposure	Risk of Infection Mean/Range (%)
Transfusion of contaminated blood	84-100
Intravenous drug use (needle sharing)	0.8
Receptive anal intercourse	0.3-0.8
Insertive anal intercourse	0.04-0.1
Occupational needlestick exposure	0.28-0.33
Insertive vaginal intercourse	0.03-0.09
Receptive vaginal intercourse	0.005-0.02
Insertive oral intercourse	0.003-0.008
Receptive oral intercourse	0.006-0.02

What cofactors make HIV infection more likely?

- STDs
- uncircumcised male
- use of hormonal contraceptives (increased exposure of endocervix)
- male +ve with female -ve
- anal sex > vaginal sex > oral sex
 - receptive anal >> insertive anal
 - insertive vaginal >> receptive vaginal
 - receptive oral >> insertive oral

Why is the risk of HIV higher with STDs?

- 1) modes of transmission are similar
- 2) both genital ulcers (syphilis, chancroid, herpes, etc) and non-ulcerative STDs (gonorrhea, Chlamydia, trichomoniasis) facilitate HIV transmission

What is the effect of antiretroviral therapy on infectiousness?

- lower blood HIV levels are associated with lower transmission rates
- but, HAART DOES NOT make HIV pts non-infectious (still need to practice safe sex even if on Rx)

What is the effect of circumcision on HIV risk?

- decreases risk of acquiring STDs & HIV
- preputial skin contains many cells susceptible to HIV infection
 - helper T lymphocytes, monocyte/macrophage cells, Langerhans cells, follicular dendritic cells

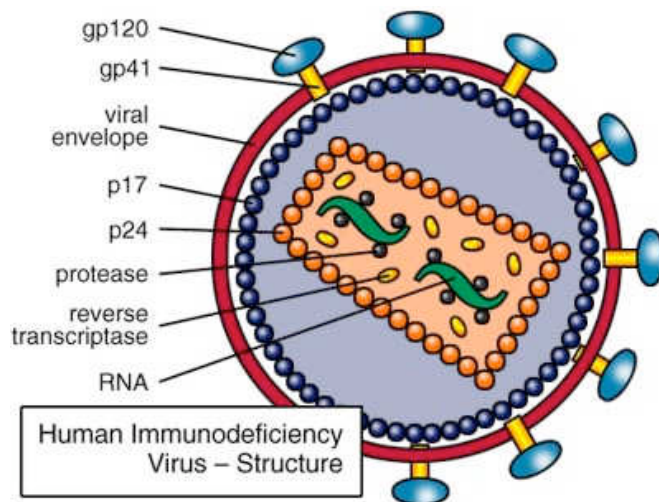
HIV VIROLOGY

How many HIV viruses are there?

- **HIV-1 is most common**
- HIV-2 is less virulent and accounts for very few cases

What is the HIV virus?

- spherical shape
- outer viral envelope
- variable surface projections (gp120 and gp41)
- icosahedral capsid with ribonucleoprotein complexed with a core shell
- 2 single-stranded viral RNA + reverse transcriptase + protease + integrase



Describe the HIV replication cycle.

- HIV binds to CD4 receptor on susceptible host cells (dendritic cells, macrophages, helper T cells, etc)
 - can also attach to CCR5 and CXCR4 co-receptors
- fusion of viral and cell membranes allows entry
 - mediated by **gp120 transmembrane protein**
- after fusion, virus is uncoated by proteolytic event
 - mediated by **protease**
- after entry, viral RNA is converted to double-stranded DNA
 - mediated by **reverse transcriptase within cytoplasm**
 - this process of reverse transcription occurs within 4-6 hrs of infection
- viral DNA is then transported into nucleus and integrated into host cell chromosomal DNA
 - integration is mediated by **integrase**
- provirus then uses host cell transcription/translation machineries to make its own gene product
 - involves RNA polymerase II, transcription factors, ribosomes, etc

Name 2 key HIV-encoded proteins involved in upregulation of viral gene expression and replication.

- Tat
- Rev

Name 4 HIV accessory proteins crucial in determining HIV virulence?

- Nef
- Vif
- Vpu
- Vpr

PATHOGENESIS OF HIV INFECTION

What is the natural history of HIV infection?

→ **highly variable course**

- without Rx, the typical course runs over 8 to 12 yrs
- without Rx, median time between infection and development of AIDS is 10-11yrs
- **three distinct phases are defined:**
 - 1) primary infection } events in this stage determine pattern/rate of disease progression
 - 2) chronic asymptomatic infection
 - 3) overt AIDS
- **3 types of patients:**
 - a) typical progressors } 60-70%
 } develop AIDS in ~10yrs after infection
 - b) rapid progressors } 10-20%
 } develop AIDS in <5yrs after infection
 - c) slow progressors } 5-15%
 } develop AIDS >15yrs after infection
 } non-progressors are a subgroup (1%)

How do you diagnose primary HIV infection?

- 3 laboratory findings } a) **high viral load** (>1 million HIV RNA copies/mL)
 b) **↓ in blood CD4+ T cell count**
 c) **large ↑ in blood CD8+ T cell count**
- decrease in viral load coincides with end of acute primary infection syndrome
→ evidence of HIV-specific immune responses
- **standard lab tests are usually negative during acute infection**

How does primary HIV infection present?

- **transient symptomatic illness of variable severity } occurs in 40-90%**
→ may mimic mononucleosis or other acute febrile illnesses
→ fatigue, fever, night sweats, skin rash, lymphadenopathy, myalgia, arthralgia
- signs and symptoms appear 2-4 wks after infection
- **self-limited syndrome that lasts <14days**

What is the HIV virological set point?

- during transition from primary infection to chronic infection, HIV plasma RNA levels reach a virologic set point that predicts rate of disease progression
- virologic set point varies among HIV-infected individuals
→ tends to remain stable in the same person during the chronic phase
- **viral load is the most accurate predictor of disease progression**

How does the chronic asymptomatic infection phase present?

- **long phase of clinical latency } usually lasts ~10yrs**
- no signs or symptoms
- relatively stable replication levels and CD4+ T cell counts
→ viral load & CD4+ counts stay stable in blood, but virus replication and accumulation of extracellular virus trapped in follicular dendritic cell network are active

How does the overt AIDS phase present?

- **rapid increases in viral load + rapid drop in CD4+ T cell counts (<200-300 cells/μL)**
- appearance of constitutional symptoms
- may also develop AIDS-defining opportunistic infections or malignancies
→ without treatment, AIDS usually leads to death in 2-3 yrs
→ risk of death significantly higher when CD4+ counts are <50 cells/μL

How does HIV escape the host immune response?

- 1) virologic mechanisms } early formation of a **stable pool of latently infected CD4+ T cells**
containing HIV that is capable of replicating
→ sheltered from immune system and HAART
→ major obstacle to HIV eradication & long-term control of replication
} genetic variability of HIV
→ intrinsic ability of virus to mutate rapidly
} trapping of infectious virions on surface of follicular dendritic cells
- 2) immunologic mechanisms } deletion of HIV-specific CD4+ T cell clones
} deletion of HIV-specific cytotoxic CD8+ T clones
} generation of virus escape mutants
} egress of cytotoxic T lymphocytes from LNs
} impaired function of APCs
} interference with humoral neutralizing response

Can HIV be eradicated?

→ **not possible with current meds**

- eradication is only possible if HIV replication is completely & sustainably suppressed and if there were no pool of long-lived, latently infected cells to serve as a reservoir
- free HIV virion are eliminated with $T_{1/2} = 6\text{hrs}$
- productively infected cells have $T_{1/2} = 1.6\text{days}$
- unfortunately, latent pool of HIV-infected CD4+ T cells has $T_{1/2}$ of 3-6 months
→ this reservoir originates from productively infected cells during primary infection
→ this pool represents a major obstacle to HIV eradication

What tissues can serve as HIV sanctuaries?

- sanctuaries = tissue that shelters HIV or where HAART can't achieve therapeutic []'s
- serve as reservoir of latently infected cells and as potential source of virus replication
- 1) lymphoid tissue
- 2) genital organs
- 3) mucosa-associated lymphoid tissue
- 4) CNS

DIAGNOSIS AND MONITORING OF HIV

What are the 3 categories of tests for diagnosis & monitoring of HIV infection?

- 1) diagnostic tests
 - **reactive HIV ELISA**
 - HIV antibody detection in serum, blood, saliva, urine
 - Ab's can be detected as early as 3wks in some pts } by 6wks in most
 - newer tests have sensitivity & specificity ~100%
 - still need to do confirmatory Western blot (immunoblot)
 - **HIV RNA assays**
 - can detect by day 12 after infection } less specific
- 2) viral load
 - HIV RNA assays } **mainly used to monitor viral load**
 - plasma HIV RNA levels correlate with clinical stage and risk of progression
 - nadir of viral load while on HAART is a marker of duration of suppression
 - regular monitoring facilitates timely detection of drug-resistant HIV
- 3) resistance assays
 - genotypic assays } detection of drug-resistant mutations
 - phenotypic assays } estimates [] of antiviral meds needed to inhibit viral replication
 - recommended to guide selection of salvage therapy

UROLOGIC MANIFESTATIONS OF HIV INFECTION

List some non-malignant GU manifestations of HIV.

→ “SUPER SOFT HIVAN”

- **STDs** (syphilis, Chancroid, herpes, etc)
- **Urethritis** (gonorrhea, Chlamydia, etc)
- **Prostatitis**
- **Epididymitis** (CMV, toxoplasmosis, etc)
- **Renal infections** (TB, CMV, etc)
- **Stones**
- **Orchitis** (CMV, toxoplasmosis, etc)
- **Fournier’s gangrene**
- **Testicular atrophy**
- **Hematuria**
- **Impetigo**
- **Voiding dysfunction** (AUR, OAB, BOO, etc)
- **Abscesses**
- **Nephropathy** (HIVAN)

List some malignancies associated with HIV.

→ “Catch Kaposi’s PALS Live on MTV”

- **Cervical Ca**
- **Kaposi’s sarcoma**
- **Penile Ca**
- **Anal Ca**
- **Lymphoma** (NHL, Hodgkins, primary CNS, etc)
- **Skin Ca** (non-melanomatous)
- **Lung Ca**
- **Myeloma**
- **Testicular Ca**
- **Vulvar Ca**

List some non-malignant GU manifestations of HIV?

- ## What opportunistic infections are considered AIDS-defining illnesses?

- multiple bacterial infections in kids (<13yrs)
- fungal infections } URT candidiasis, non-pulmonary coccidiomycosis/cryptococcosis/histoplasmosis
- CMV (retinitis, etc)
- mycobacterium avium complex (MAC)
- Pneumocystis carinii pneumonia (PCP)
- TB in any site
- toxoplasmosis of the brain
- recurrent pneumonia
- salmonella sepsis
- HSV lasting >1month

Malignant Conditions

What are some malignancies associated with HIV infection?

- 1) **Kaposi's sarcoma** } 1000x more common than general population
 → especially high in gay men with HIV
 } associated with **HHV-8**
 } classic and epidemic (HIV) forms
 } usually present w/ disseminated skin lesions + LN & visceral disease
 → can have macular lesions, plaque lesions, or nodular lesions
 } survival depends on CD4 counts
 Rx → HAART
 → cutaneous lesions } Rads, laser, cryo, anti-neoplastic injections
 → chemo } vincristine, vinblastine, bleomycin, doxorubicin, -taxels
- 2) **NH lymphoma** } 100x more common than general population
 → **most common AIDS-associated cancer among patients on HAART**
 } usually present with advanced disease with systemic symptoms
 → short median survival (5-10 months after Dx)
 Rx → usual CHEMO for NHL
- 3) Hodgkin's lymphoma
- 4) primary CNS lymphoma
- 5) invasive cervical Ca
- 6) vulvar Ca
- 7) high-grade anal epithelial lesions
- 8) **penile Ca**
- 9) non-melanomatous skin cancer
- 10) myeloma
- 11) lung carcinoma
- 12) **testicular Ca (GCTs, NGCTs, lymphoma)**
 } 50x more common than gen. pop. } more commonly bilateral
 } high-grade testicular lymphoma more common
 Rx → Sx, RADS, CHEMO } must consider immunosuppressive effects of RADS & CHEMO

Which non-infectious diseases are considered AIDS-defining illnesses?

- Kaposi's sarcoma
- primary CNS lymphoma
- systemic intermediate/high-grade B-cell NH lymphoma
- invasive cervical Ca
- progressive multifocal leukoencephalopathy
- HIV encephalopathy

OCCUPATIONAL RISKS

How common is occupational HIV infection?

- uncommon } most are from hollow-bore injection needle-stick injury
- } few cases from mucous membrane exposure
- } no cases from needle-stick with solid surgical needle

What are the RFs for occupational HIV infection?

- 1) deep exposure (vs superficial)
 - 2) blood visible on device causing exposure
 - 3) device had been placed in source-patient's vein or artery
 - 4) source-patient died within 60 days of exposure (terminal)
 - 5) exposed health care worker didn't take post-exposure chemoprophylaxis (zidovudine)
- \ related to increased
/ inoculum

What is the risk of HIV infection from an occupational needle-stick exposure?

- about 0.3%

What is the recommended management once HIV exposure has occurred?

- 1) allow exposed site to bleed
- 2) clean & decontaminate wound } soap and water, then disinfectant
- 3) post-exposure prophylaxis } **reduces risk of HIV transmission by ~80%**
 - } 3-drug regime for severe exposures
→ zidovudine + lamivudine + 1 of 4 additional agents
 - } 2-drug regime for lesser exposures
→ zidovudine + lamivudine or additional agent

What factors determine the need for post-exposure prophylaxis?

- nature of exposure
- viral load in patient
- volume of blood or fluid
- potential for resistant strains in patient

What is the issue with post-exposure prophylaxis?

- 1) high toxicity } often limits completion of regimen
- 2) documented evidence of failures

ANTIRETROVIRAL THERAPY

How do you Dx HIV/AIDS prior to discussing therapy?

- 1) **HIV ELISA test (anti-HIV Ab's)**
 - repeat ELISA x 2 to make sure no false +ve's
 - confirm with Western blot analysis
- 2) **AIDS-defining illnesses**

What is the goal of anti-retroviral therapy?

- maximal & sustained suppression of HIV replication
- prevent disease progression & prolong survival while maintaining QOL
 - keep HIV RNA viral load <50 copies/mL

What is the best way to monitor anti-retroviral therapy for HIV?

- 1) plasma HIV RNA levels (viral load)
- 2) CD4+ lymphocyte count
 - **initial treatment should result in undetectable plasma HIV RNA levels within 4-6 months accompanied by a concomitant rise in CD4+ counts**
 - undetectable viral load DOES NOT MEAN virus eradication } latent pools and sanctuaries

What are the different classes of HIV medications (CHART)?

- 1) nucleoside reverse transcriptase inhibitors (NRTIs)
 - first introduced in 1987 as monotherapy
 - blocks viral DNA elongation by **stopping addition of further nucleosides**
 - competitive inhibitor of reverse transcriptase
 - 6 nucleoside RTIs } zidovudine, didanosine, zalcitabine, stavudine, lamivudine, & abacavir
- 2) nucleotide reverse transcriptase inhibitors
 - 1 nucleotide RTI } tenofovir
- 3) protease inhibitors (PIs)
 - introduced in 1995
 - **bind & block protease (results in release of immature, noninfectious viral parts)**
 - **can also act on chronically infected cells**
 - 6 PIs } saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, & lopinavir
- 4) non-nucleoside reverse transcriptase inhibitors (NNRTIs)
 - introduced in 1996
 - competitive inhibitor of reverse transcriptase
 - 3 NNRTIs } nevirapine, delavirdine, & efavirenz

What is HAART?

- “highly active anti-retroviral therapy”
- most regimes are based on **2 NRTIs + either an NNRTI or a PI**
- triple NRTI regimes are being used more often because they are easy to administer and allow deferred use of NNRTIs and PIs
- can develop central obesity, dorsal fat pad (buffalo hump), breast enlargement, etc

What are the urologic side effects of RTIs?

- mitochondrial toxicity
- lactic acidosis
- zalcitabine (NRTI) } peripheral neuropathy
- } painful penile ulcers

What are the urologic side effects of PIs?

- hypoglycemia
- ritonavir } high risk of bleeding
- indinavir } stones

Which factors determine the timing of initial therapy?

- 1) symptoms
 - symptomatic } treatment ASAP
 - asymptomatic } depends on CD4+ lymphocyte count & HIV RNA load
 - CD4+ count is an immediate predictor of prognosis**
 - viral load indicates level of actual HIV replication (progression)**
- 2) patient's commitment to therapy
- 3) patient's knowledge of the limitations of current regimes

What are some new strategies being investigated to eradicate HIV?

- 1) therapeutic vaccination
- 2) structured treatment interruption
- 3) transfer of HIV-specific cell populations to enhance cell-mediated immunity
- 4) transfer of pooled immune sera from donors who have HIV infection
- 5) transfer of monoclonal Ab's directed against HIV

What are the indications for HIV testing?

- evaluation of blood and organs for donation
- persons at risk for HIV
 - STD, hx of illegal IV drug use, others who consider themselves at risk
 - hx of sexual contact w/ homosexual men, multiple unsafe heterosexual contacts
 - hx of needle sharing
 - sexual contact w/ pt w/ HIV
- pts w/ unscreened blood transfusion since 1977
- hx of STDs including hep B
- hx of symptoms associated w/ HIV infection
- active TB
- selected women of reproductive age living in community w/ high HIV prevalence
- children of HIV+ mothers

Chapter #13 – Cutaneous Diseases of the External Genitalia

INTRODUCTION TO BASIC DERMATOLOGY

What are the 3 layers of the skin?

- 1) epidermis } stratified squamous epithelium
- 2) dermis } thin superficial layer (papillary dermis) \ collagen, elastin, and
 } thicker deep layer (reticular dermis) / reticular fibers
- 3) subcutaneous tissue

What are the important characteristics of cutaneous lesions of the external genitalia?

- Primary lesions
 - 1) color } red, brown, black, yellow, blue, green
 - 2) morphology } macule, papule, plaque, nodule, pustule, vesicle, bulla, wheal
- Secondary lesions
 - 1) morphology } scale, crust, erosion, ulcer, atrophy, scar

What are the different morphologies of cutaneous lesions (CHART)?

- Primary lesions
 - macule } flat circumscribed discoloration
 - papule } elevated solid lesions <5mm
 - nodule } elevated solid lesions >5mm
 - vesicle } fluid-filled collection <5mm
 - bulla } fluid-filled collection >5mm
 - pustule } collection of leukocytes and fluid (pus)
 - wheal (hive) } firm erythematous plaque from infiltration of dermis with fluid
- Secondary lesions
 - scale } excess dead epidermal cells produced by abN keratinization and shedding
 - crust } collection of dried serum & cellular debris (scab)
 - erosion } focal loss of epidermis only that heals without scarring
 - ulcer } focal loss of epidermis + dermis that heals with scarring
 - fissure } linear loss of epidermis + dermis with sharply defined, vertical walls
 - atrophy } depression in skin from thinning of epidermis or dermis
 - scar } abN formation of connective tissue (dermal damage)

What are some common laboratory tests used to confirm the Dx of cutaneous lesions?

- KOH } shows fungal hyphae (dermatophytes, Candida, etc)
- Tzanck smear } shows viral agents (HSV, varicella-zoster, molluscum contagiosum, etc)

DERMATOLOGIC THERAPY

List the different TOPICAL therapies for cutaneous lesions of the external genitalia.

→ active ingredient + vehicle

- 1) emollients } water & lipids for dry skin
- 2) anti-inflammatory agents } corticosteroids
- 3) antibiotics
- 4) antifungals
- 5) chemotherapeutic agents

List some of the local effects of topical corticosteroids.

- epidermal atrophy (reversible in most cases)
- telangiectasia
- hypopigmentation
- allergic reactions
- altered course of skin infections & infestations

List the different SYSTEMIC therapies for cutaneous lesions of the external genitalia.

- 1) antibiotics
- 2) antifungals } ketoconazole, fluconazole
- 3) antivirals
- 4) anti-inflammatories } steroids
- 5) anti-pruritic agents
- 6) chemotherapeutic agents } MTX, cyclophosphamide
- 7) immunosuppressants } azathioprine, cyclosporine, tacrolimus

What are the important pharmacokinetics of systemic steroids?

- absorbed in jejunum
- peak concentration in 30-90mins
- $T_{1/2} = 1-5\text{hrs}$

List some of the long term side effects of systemic steroids.

- osteoporosis
- DM
- AVN of the hip
- HTN
- obesity
- immunosuppression
- cataracts
- psychiatric changes

List the different ENERGY MODALITIES used for cutaneous lesions of the external genitalia.

- 1) UV light therapy (UVA, UVB)
- 2) photodynamic therapy
- 3) laser therapy
- 4) cryosurgery

List the common cutaneous disorders of the external genitalia.

- ALLERGIC eg eczema, contact dermatitis, erythema multiforme
- PAPULOSQUAMOUS eg psoriasis, Reiter's syndrome, lichen planus, lichen sclerosus, fixed drug eruptions, seborrheic dermatitis
- VESICOBULLOUS eg bullous pemphigoid, pemphigous vulgaris, dermatitis herpetiformis, benign familial pemphigoid (Hailey-Hailey)
- ULCERATIVE (infectious vs non-infectious) eg aphthous ulcers, Behcet's disease, pyoderma gangrenosum, traumatic
- INFECTIOUS eg STDs, balanoposthitis, cellulitis, Fournier's gangrene, folliculitis, furunculosis, Hidradenitis suppurativa, Trichomycosis axillaris, erythrasma, ecthyma gangrenosum, candidal intertrigo, dermatophyte infections, pedunculosis pedis, scabies
- NEOPLASTIC eg Bowen's/Erythroplasia of Queyrat, SCC, bowenoid papulosis, verrucous carcinoma (Buschke-Lowenstein), BCC, Kaposi's, Pseudoepitheliomatous Keratotic & Micaceous Balanitis, melanoma, extra-mammary Paget's disease, cutaneous T-cell lymphoma
- MISCELLANEOUS eg skin tag, epidermoid cysts, seborrheic keratosis, lenigo simplex, mole (nevus), dermatofibroma, neurofibroma, capillary hemangioma, vitiligo

What is the work-up for a skin lesion of the external genitalia?

- 1) History
 - duration, pain, pruritis, asymptomatic
 - prodrome (URTI, GI infection, eye issues, etc), sexual exposures, LUTs, dysuria, trauma hx
 - extra-genital lesions
 - systemic symptoms } fever
 - household members, contacts with similar features
 - PMHx } known skin or systemic disease (IBD, crohn's, DM, malignancies, etc)
 - FmHx
 - travel history
 - meds, allergies
- 2) Physical exam
 - general, vitals
 - circumcised
 - description of lesion, #, location, pigmentation, discharge, etc
 - perineal exam
- 3) investigations
 - Bx
 - gram stain, C&S
 - KOH test
 - Darkfield exam (syphilis)
 - serology
 - Tzanck prep (HSV, molluscum)

ALLERGIC DERMATITIS

What is the DDx of allergic dermatitis (CHART)?

- eczema
- contact dermatitis (allergic vs irritant)
- seborrheic dermatitis
- intertrigo
- balanoposthitis
- Zoon's balanitis
- Candidal-related illness
- impetigo
- Herpes simplex, Herpes zoster
- drug reaction

What are some common allergic "eczematous" lesions of the external genitalia?

→ allergy-mediated processes leading to pruritic skin lesions

1) **atopic dermatitis (eczema)**

- erythematous papules + thin plaques + secondary excoriations
→ **intense pruritus is hallmark** } scratching can lead to superinfection w/ *S. aureus*
- 90% present before age 5 } usually have +ve FmHx
- trigger factors include chemicals, detergents, dust mites
- extra-genital involvement common } assoc'd w/ asthma, allergic rhinitis, nasal polyps
- Rx → gentle cleaning with non-alkali soaps + emollients
→ short course of topical steroids +/- anti-histamines
→ systemic steroids, MTX, cyclosporine for rare severe widely disseminated cases

2) contact dermatitis

- irritant contact dermatitis (80%) VS allergic contact dermatitis (20%)
- **well demarcated area** corresponds to area of skin exposed to irritant or allergen
- occupational irritants common; nickel dermatitis most common allergen
- Rx → avoid skin contact with irritant + skin barriers (emollients, ointments)
→ patch testing for allergens + anti-histamines

3) erythema multiforme & Stevens-Johnson syndrome

→ **targetoid lesions**

- erythema multiforme minor
 - abrupt onset of symmetrical fixed red papules (may evolve into target lesions)
 - commonly involves oral mucous membranes
 - most cases precipitated by HSV type 1 and 2
 - erythema multiforme major (aka Stevens-Johnson syndrome)
 - like extensive skin burns, and if severe, may mimic toxic epidermal necrolysis
→ erythema & erosions of labia, penis, perianal region
 - commonly have **prodromal upper respiratory illness**
 - **most cases incited by drug exposures**
→ NSAIDs, sulfonamides, tetracycline, penicillin, doxycycline, etc
- Rx → EM minor is self-limiting (resolves in 3-4 wks) } anti-histamines for symptoms
→ **EM major has 30% death rate** } stop offending drug + supportive care (4-6wks)
- can get complications from scarring } joint contracture, vaginal stenosis, urethral meatal stenosis, anal strictures



→ ECZEMA OF THE GENITALIA



→ CONTACT DERMATITIS



→ ERYTHEMA MULTIFORME (MINOR) } targetoid lesions of hands & penis

PAPULOSQUAMOUS DISORDERS

What is the DDX of papulosquamous lesions (CHART)?

- psoriasis
- Reiter's syndrome
- lichen planus
- fixed drug eruption
- seborrheic dermatitis
- Bowen's disease
- 2° syphilis
- erythrasma
- pityriasis rosea & pityriasis versicolor
- discoid lupus
- mucosis fungoides
- extra-mammary Paget's disease
- dermatophyte infection

What are some common papulosquamous lesions of the external genitalia?

1) **Psoriasis**

- well demarcated, pruritic, erythematous plaque with **silvery scales**
→ often seen over elbows, knees, buttock, nails
- triggers include trauma, infection, stress, new meds
- bimodal onset (during 20's and 50's) } **1/3 have +ve family hx**
- common to get genital involvement
- Rx → low dose topical steroids for genital psoriasis } short courses only
→ PUVA contraindicated due to risk of genital squamous cell carcinoma
→ systemic MTX, cyclosporine, retinoids for extensive psoriasis

2) **Reiter's syndrome**

- **urethritis + arthritis + conjunctivitis/uveitis + oral ulcers + skin lesions**
- more common in M and more common among HIV +ve patients } +ve HLA-B27
- preceded by episode of urethritis (*Chlamydia*, *N. gonorrhoeae*) or GI infection (*Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, etc)
- genital skin lesions ("**circinate balanitis**") resemble psoriasis
- lesions on palms & soles } "**keratoderma blenorrhagicum**"
- Rx → genital Reiter's is self limited } +/- topical steroids (short course, low dose)

3) **Lichen Planus**

- idiopathic inflammatory disease } epidermal basal cell damage + massive infiltration of **mononuclear cells** in papillary dermis
- involves flexor surfaces, trunk, lumbosacral area, oral mucosa AND glans penis
→ on genitalia can present as papules (isolated or grouped), white reticular pattern or ring-like arrangement w/ or w/o ulceration
- Rx → **spontaneous resolution seen in 2/3 of cases** } oral form usually persists longer
→ topical steroids if pruritic } if more severe, systemic steroids, cyclosporine, metronidazole, griseofulvin, etc
→ Bx is necessary to r/o malignancy if suspicious, especially if ulceration present

4) **Lichen Nitidus**

- inflammatory eruption of tiny, discrete, flesh-colored papules in large clusters
→ well-circumscribed, lymphohistiocytic infiltrate
- involves flexor surfaces, trunk, dorsum of hands, nails, AND genitalia
- Rx → spontaneous resolution seen in most patients
→ topical steroids if pruritic +/- anti-histamines

5) **Lichen Sclerosus et Atrophicus (aka BXO)**

- chronic inflammatory disease with predilection for external genitalia
- tissue pallor + hyperkeratosis } commonly involves glans penis & foreskin in M
} commonly involves perianal area in F
→ for those with genital disease, 15-20% have extra-genital disease
- 6-10x more common in F
- **risk of squamous cell carcinoma**
- Rx → topical steroids (long courses OK for LS) } circumcision for males with phimosis
→ r/o urethral strictures
→ Bx to r/o malignant change (also confirms Dx)

6) Fixed drug eruptions

- usually occurs **1-2 wks after first exposure** } sulfonamides, NSAIDs, barbiturates, OCP, tetracyclines, salicylates, etc
 - reaction occurs in same location after subsequent exposures to meds
- involves lips, face, hands, feet, AND genitalia
 - **solitary inflammatory plaques on shaft or glans** } may be erosive & painful
- Rx → removal of offending agent } may leave brown pigmentation

7) seborrheic dermatitis

- common skin disease that presents with sharply demarcated pink-yellow to red-brown plaques with flaky scale } similar to eczema & psoriasis
- **involves areas w/ sebaceous glands** } scalp, eyebrows, nasolabial folds, ears & genitalia
- more common in Parkinson's disease and AIDs } if severe, consider HIV testing
- may involve autoimmune response to normal yeast flora *Malassezia furfur*
- Rx → topical antifungal creams have 75-90% response rates
 - for hair-bearing areas, dandruff shampoos (zinc, salicylic acid, selenium sulfide)

What is the DDx of Lichen planus (LP) on the genitalia?

- SCC
- Bowen's disease
- Zoon's balanitis
- psoriasis
- 2° syphilis
- SLE

What is the DDx of a fixed drug eruption lesion on the genitalia?

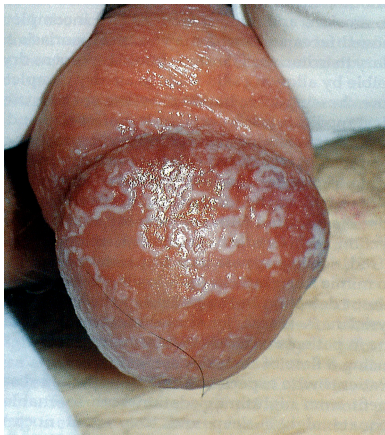
- herpes simplex
- insect bite



→ GENITAL PSORIASIS



→ GENITAL PSORIASIS



→ REITER'S SYNDROME (balanitis circinata)



→ REITER's SYNDROME (keratoderma blennorrhagicum)



→ GENITAL LICHEN PLANUS



→ GENITAL LICHEN SCLEROSIS ET ATROPHICUS (BXO)



→ FIXED DRUG ERUPTION ON GENITALIA

VESICOBULLOUS DISORDERS

What is the DDx of vesicobullous disorders (CHART)?

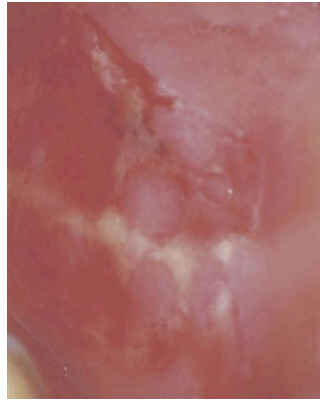
- bullous pemphigoid
- pemphigus vulgaris
- pemphigus foliaceus
- dermatitis herpetiformis
- benign familial pemphigoid (Hailey-Hailey disease)
- Zoon's balanitis
- contact dermatitis
- porphyria cutanea tarda
- herpes simplex
- herpes zoster
- lymphangioma circumscriptum
- fixed drug eruption
- trauma (innocent vs factitial)
- Behcet's syndrome
- impetigo

What are some common vesicobullous disorders of the external genitalia?

- 1) bullous pemphigoid
 - autoimmune **SUB-epidermal** blistering disease } more common in older M
→ auto-Ab's directed against proteins involved in cell-cell adhesion
→ **deposition of IgG antibodies seen along BM**
 - non-bullous phase followed by tense blisters
 - forms over flexor surfaces, inner thighs AND genitalia
 - Rx → systemic steroids + immunosuppressants
→ severe, treatment resistant cases get IVIG or plasmapheresis
- 2) pemphigus vulgaris
 - autoimmune **INTRA-epidermal** blistering disease
→ auto-Ab's directed against keratinocyte cell surface markers & desmosomes
 - all get painful oral erosion + 50% have skin blisters } **Asboe-Hansen sign** (spreading of fluid under N adjacent skin)
 - can be fatal if untreated due to loss of epidermal barrier function of large areas of skin
 - Rx → systemic steroids +/- azathioprine, cyclophosphamide
- 3) dermatitis herpetiformis & linear IgA bullous dermatosis
 - autoimmune blistering diseases associated with deposition of IgA antibodies at BM
 - dermatitis herpetiformis is skin manifestation of celiac disease } associated with gluten allergy
- pruritic plaques, papules, and vesicles in symmetrical distribution
Rx → dapsone + gluten restricted diet
 - linear IgA bullous dermatosis
- linear vesicles & bullae in linear and circumferential pattern
Rx → dapsone or sulfapyridine } long-term spontaneous remission occurs in 30-60%
- 4) benign familial pemphigoid (Hailey-Hailey disease)
 - **autosomal dominant (AD) blistering disease** with predilection for intertriginous areas
→ groin, axilla, infra-mammary folds
 - pruritic, painful, foul-smelling confluence of vesicles & blisters
 - may have super infection with yeast or bacteria
 - Rx → avoid friction & sweating
→ topical or intralesional steroids (low-dose, short courses)
→ if resistant to meds, try wide excision + graft or dermabrasion, laser vaporization



→ BULLOUS PEMPHIGOID
- SUB-epidermal blisters (IgG deposits on BM)



→ PEMPHIGUS VULGARIS
- INTRA-epidermal blisters
(painful oral erosion)



→ LINEAR IgA BULLOUS DERMATOSIS } circumferential & linear vesicles



→ HAILEY-HAILEY DISEASE

NON-INFECTIOUS ULCERS

What is the DDx of genital ulcers (CHART)?

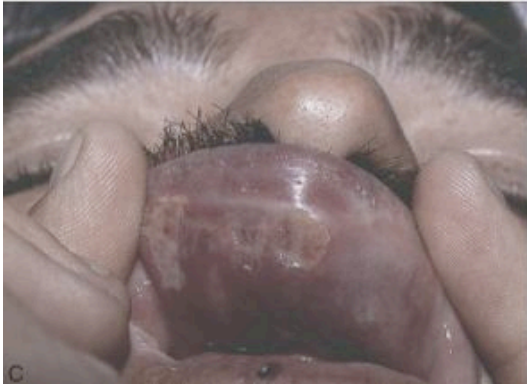
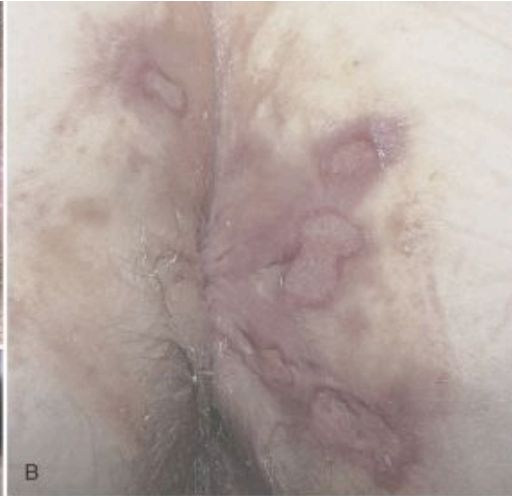
- Syphilis
- Chancroid
- Herpes simplex
- Lymphogranuloma venereum
- aphthous ulcer
- Behcet's disease
- pyoderma gangrenosum
- granuloma inguinale
- Crohn's disease
- leukocytoclastic vasculitis
- Wegener's granulomatosis
- factitial dermatitis

What are some common non-infectious ulcerative disorders of the external genitalia?

- 1) Aphthous ulcers & Behcet's disease
 - small, painful ulcers commonly involving mouth and occasionally the genitalia
→ consider **Behcet's if oral ulcers + genital ulcers + uveitis**
 - Behcet's common in Turkey } generalized relapsing & remitting ulcers
 } 80% have ocular findings & can lead to blindness
 } may get epididymitis, aneurysms, DVTs, GI issues, arthritic problems, neurologic issues
 - Rx → topical and systemic steroids, dapsone, colchicines, immunosuppressants
- 2) Pyoderma gangrenosum
 - **ulcerative skin disease assoc'd w/ IBD, arthritis, collagen vascular disease, myeloproliferative disorders**
→ 20-50% are idiopathic
 - affects F more often with likely autoimmune pathogenesis
 - **painful** skin & mucous membrane ulcers } **extensive loss of tissue + purulent base**
 - genital involvement uncommon } penis, scrotum, vulva, peristomal sites
 - Rx → **topical & systemic steroids** +/- immunosuppressants
- 3) traumatic causes of ulcers
 - accidental vs self-inflicted (factitial dermatitis)

How do you make the Dx of Behcet's disease?

- based on Behcet's International Study Group
- recurrent oral ulcers + 2 of any of the following:
 - recurrent genital ulcers
 - eye lesions
 - skin lesions
 - skin sensitivity to needles (pathergy test)



→ BEHCET'S DISEASE } A – scrotal B – perianal C - oral



→ PYODERMA GANGRENOSUM

INFECTIONS AND INFESTATIONS

What are the different STDs that cause genital cutaneous lesions (CHART)?

- 1) syphilis
- 2) chancroid
- 3) herpes simplex
- 4) lymphogranuloma venereum
- 5) granuloma inguinale
- 6) molluscum contagiosum
- 7) HPV (condyloma acuminata)

What are some common infectious lesions of the external genitalia?

- 1) STDs
 - see above
- 2) balanitis & balanoposthitis
 - in kids, bacterial infections are the most common cause
 - in adults, cause can be intertrigo, irritant contact dermatitis, local trauma, candidal or bacterial infections
 - Rx → removal of irritant, improved hygiene, topical ABx, topical antifungals
 - occasionally short course of low-dose steroids
 - Cx in select cases
 - if refractory to meds, consider malignancy, Zoon's balanitis, psoriasis, etc
- 3) cellulitis & erysipelas
 - erysipelas is a superficial bacterial skin infection limited to **dermis + lymphatics**
 - often involves the face
 - raised & distinct border
 - cellulitis is an infection of **deep dermis & subcutaneous tissues**
 - most commonly due to gram +ve's (*S. pyogenes*, *S. aureus*)
 - often not raised & no distinct border
 - may see "rubor, calor, dolor, tumour"
 - Rx → systemic ABx with gram +ve coverage } more broad-spectrum coverage in DM
- 4) Fournier's Gangrene
 - aka necrotizing fasciitis of the perineum
 - **most commonly mixed bacterial flora } gram +ve, gram -ve, and anaerobes**
 - rapid progression from cellulitis to blister formation to foul-smelling necrotic lesions
 - spreads along fascial planes, so skin may only be the tip of the iceberg
 - often have pain out of proportion to visible extent of infection
 - xray or CT may show gas bubbles
 - mortality rate high as 15-40%
 - Rx → broad-spectrum ABx + early extensive surgical debridement
 - may need 2nd look after 24-48hrs
 - testes can be spared due to different blood supply
- 5) Folliculitis
 - perifollicular pustules on erythematous base } most common on hair-bearing areas (scalp, beard, groin, buttocks, etc)
 - associated w/ local trauma (shaving, rubbing) & contaminated hot tubs, pools, etc
 - *S. aureus*, *Pseudomonas aeruginosa*, fungi, herpes simplex
 - Rx → good hygiene + removal of offending irritants
 - topical or systemic ABx, anti-viral, or anti-fungals
- 6) Furunculosis
 - abscess associated with a hair follicle
 - common in groin & buttocks } *S. aureus* is most common pathogen
 - Rx → warm compresses
 - ABx if associated cellulites present
 - I & D if larger

- 7) Hidradenitis suppurativa (acne inversa)
 - abscesses & sinuses associated with blocked hair follicles that rupture into dermis
 - **bacterial infection NOT the primary initiator**
 - painful inflamed nodules + **sterile abscesses** +/- draining sinuses
 - common in axilla, groin, perianal area, and infra-mammary areas
 - serious complications can occur } hypoproteinemia, 2° amyloidosis, urethral fistulae, bladder fistulae, rectal fistulae
 - **risk of SCC in areas of heavy scarring**
 - Rx → improved hygiene + wt loss + minimize moisture
 - topical clindamycin
 - systemic tetracycline
 - wide excision + skin grafts if severe } repeated I&D discouraged
- 8) Trichomycosis Axillaris & Erythrasma
 - both infections caused by **Corynebacterium**
 - Trichomycosis axillaris is a superficial bacterial infection of axillary or pubic hair
 - yellow, red, or black nodules on hair shafts + characteristic odour
 - may be associated with hyperhidrosis
 - Rx → shaving provides immediate improvement
 - po erythromycin or anti-bacterial soaps for prevention
 - Erythrasma is an infection of skin in moist areas like groin & axilla
 - red-brown scaling eruptions with sharp borders } sometimes pruritic } may resemble tinea cruris
 - bright coral-red fluorescence under wood lamp
 - Rx → anti-bacterial soap + topical cream (aluminum chloride, clindamycin, etc)
 - oral erythromycin
- 9) Ecthyma Gangrenosum
 - **skin manifestation of pseudomonal septicemia** } most common in anogenital area
 - tender group of erythematous macules that can progress to bullae or rupture
 - seen in debilitated or immunosuppressed patients
 - Rx → immediate iv anti-pseudomonal ABx } poor prognosis
 - may need wound debridement
- 10) Candidal Intertrigo
 - fungal infection of macerated skin folds
 - pruritic reddened skin with **satellite lesions**
 - pseudohyphae on KOH prep
 - Rx → improve hygiene + keep area dry
 - topical anti-fungal (imidazoles) x 2wks } occasionally oral anti-fungals
- 11) Dermatophyte infection
 - fungal infection within keratinized tissue (hair, skin, nails)
 - **3 different genera } *Trichophyton, Microsporum, Epidermophyton***
 - *tinea cruris* of the groin & genitals } “jock itch”
 - sharply demarcated lesion with raised erythematous border
 - penis and scrotum are usually spared
 - **significant scrotal involvement should raise suspicion for candidiasis**
 - Rx → improve hygiene + keep area dry
 - wt loss
 - **topical anti-fungal creams**

How do you differentiate candida from tinea cruris?

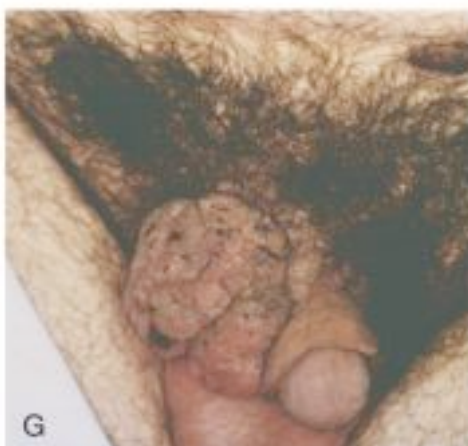
- candida } involves intertriginous areas (groin creases)
 - } satellite lesions
- tinea cruris } does NOT involve intertriginous areas
 - } NO satellite lesions

What are the RFs for Fournier's gangrene? }} DAMPPP SCROOTI

- **D**M
- **A**lcohol abuse
- **M**alnutrition
- **P**erianal disease
- **P**araphimosis
- **P**VD
- **S**urgery in local area
- **C**IC (urine extravasation)
- **R**oids
- **O**ld age
- **O**besity
- **T**rauma
- **I**mmunosuppression (eg HIV)

What are the RFs for furunculosis?

- DM
- obesity
- poor hygiene
- immunosuppression



→ GENITAL SKIN STDs } A – herpes simplex
B – molluscum contagiosum
C – syphilis
D – granuloma inguinale

E - chancroid
F – lymphogranuloma venereum
G – condyloma acuminata (HPV)



→ PENOSCROTAL CELLULITIS



→ FOURNIER'S GANGRENE



→ PSEUDOMONAL FOLLICULITIS



→ FURUNCLE



→ HIDRADENITIS SUPPURATIVA



→ TRICHOMYCOSIS AXILLARIS (*Corynebacterium*)



B
→ ERYTHRASMA (under white light)
- corynebacterium



C
→ ERYTHRASMA (under Wood's lamp)
- corynebacterium



→ ECTHYMA GANGRENOSUM } pseudomonal septic embolus

What are some common infestations of the external genitalia?

1) pediculosis pubis

- caused by crab louse } *Phthirus pubis*
→ aka “crabs” or pubic lice
 - **may coexist with other STDs } 2-fold increased risk of STDs**
 - transmission is through sexual contact } can involve contaminated clothing, sheets, towels, etc
- Rx → **5% permethrin cream** to affected hair-bearing areas x 2 applications (1wk apart)
→ **oral ivermectin** for refractory cases
→ treat all intimate contacts to prevent reinfestation
→ clean all sheets, beddings, etc

2) Scabies

- caused by female itch mite } *Sarcoptes scabiei*
 - transmission by close contact, family members, etc
 - **hallmark is severe pruritus, worse at night & after bathing**
→ small erythematous papules + thin gray/white burrows (pathognomonic)
- Rx → **5% permethrin cream** to entire body x 2 applications (1wk apart)
→ **oral ivermectin** for refractory cases
→ treat all intimate contacts to prevent reinfestation
→ clean all sheets, beddings, etc



→ PEDICULOSIS PUBIS (“crabs”)



→ SCABIES

NEOPLASTIC CONDITIONS

List some of the common neoplastic lesions seen on the external genitalia.

- 1) SCC in situ
 - Bowen's disease (shaft & perineal skin) or Erythroplasia of Queyrat (glans & prepuce)
 - usually asymptomatic but can be pruritic or painful
 - full-thickness intraepidermal carcinoma } **10% become invasive SCC**
 - overall more common in F
 - can be associated with HPV (8, 16, 39, 51)
 - Rx → Cx or local excision, topical 5-FU, YAG laser ablation, liquid nitrogen, imiquimod, etc
- 2) Bowenoid Papulosis
 - abN keratinocytes spread discontinuously on penis & vulva
 - multiple small erythematous papules forming plaques
 - resembles Bowen's disease but is **TOTALLY BENIGN**
 - associated with **HPV 16**
 - **female partners have ↑'d risk of cervical Ca } should have close f/u**
 - Rx → observation
- 3) SCC (see Chapt 31)
 - most common on glans
 - Rx → organ-preserving } brachy, EBRT, Mohs, laser ablation, limited excision
 - gold standard is partial & total penectomy
- 4) Verrucous Carcinoma (Buschke-Lowenstein)
 - locally aggressive, exophytic, low-grade variant of SCC with wart-like appearance
 - Ta SCC
 - associated with HPV types 6 and 11 (**but NOT HPV 16 nor 18**)
 - Rx → local excision } **RADs CONTRAINDICATED due to risk of malignant change**
- 5) BCC
 - most common cutaneous neoplasm overall
 - sun-exposed areas
 - genital involvement rare } scrotum & vulva
 - pearly skin-toned papule or plaque +/- telangiectases overlying it
 - low malignant potential
 - 4 different subtypes } nodular (60%), superficial, micronodular, infiltrating
 - Rx → local excision
- 6) Kaposi's sarcoma
 - tumour of reticuloendothelial system
 - slow-growing blue-red pigmented macule
 - **4 subtypes } classic, epidemic (HIV-related), immunosuppressive Rx-related, and African**
 - classic Kaposi's more common in mouth & GI tract } genital Kaposi's is rare
 - epidemic Kaposi's very common to present as solitary genital lesion } worse prognosis
 - when involving penis, can cause obstruction of meatus or fossa navicularis
 - associated with HIV patients & HHV 8
 - Rx → surgical excision, laser ablation, cryotherapy, intralesions vinblastine } usually for classic Kaposi's
 - RADs for extensive locoregional disease (15-30 Gy)
 - systemic chemo (vincristine, doxorubicin, bleomycin) for widely disseminated disease
- 7) Pseudoepitheliomatous Keratotic and Micaceous Balanitis
 - hyperkeratotic, micaceous growth on glans penis
 - may have some microscopic features of **VERRUCOUS CARCINOMA**
 - Rx → excision, laser ablation, and cryotherapy (reports of fibrosarcoma of glans after Rx)
 - aggressive treatment and close f/u } tends to recur

- 8) melanoma
 - genital melanoma very rare } pigmented macule or papule with irregular borders
 - Rx → if localized, aggressive wide excision or partial penectomy
 - if metastatic, prognosis is poor despite aggressive surgery + chemo
- 9) extra-mammary Paget's disease
 - rare intraepithelial **adenocarcinoma** of sites with apocrine glands
 - very rare in M } more common in F (vulva most common site)
 - erythematous plaque with sharp borders
 - asymptomatic, pruritic, or associated with burning pain
 - **10-30% of cases are associated with another underlying malignancy**
 - Rx → surgical excision
 - RADs and topical 5-FU or imiquimod
- 10) cutaneous T-cell Lymphoma
 - includes group of related neoplasms } mycosis fungoides, Sezary's syndrome, lymphoid papulosis, and pagetoid reticulosis
 - pruritic, plaques, erosions, ulcers, or frank skin tumours
 - chronic condition that may progress
 - **more common in HIV patients**
 - accounts for ~75% of primary skin lymphomas } B-cell derived lymphomas account for 25%
 - Rx → topical steroids, nitrogen mustard, carmustine } ~60% complete remission rate
 - RADs, PUVA, systemic chemo, IFN, retinoids

What are the RFs for SCC in situ?

- HPV
- ionizing radiation
- immunosuppression
- thermal injury
- arsenic exposure
- chronic dermatoses
- BXO

What are the RFs for penile cancer (SCC)? } } } Penile Cancer Has BURST

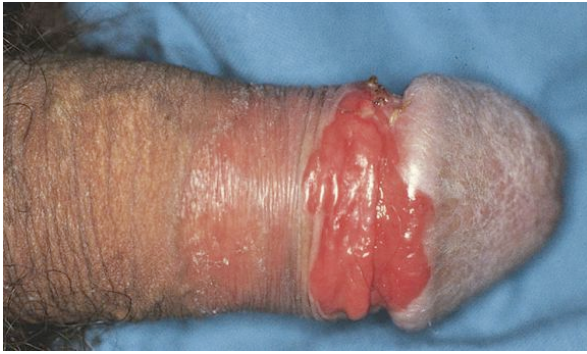
- Phimosis
- CIS
- Hygiene (poor)
- Beware Causes Penile Ca Later } BXO, Cutaneous horn, PMKB, Condyloma acuminatum, Leukoplakia
- UnCx'd patients → smegma related? (byproduct of bacterial action on desquamated cells)
 - adult Cx doesn't decrease risk
- Rads
- Smoking, chewing tobacco
- Trauma (penile)

Name the premalignant cutaneous lesions of the penis? } } **Beware Pinkus Causes Penile Cancer Later**

- | | | |
|---|---|---------------------------|
| → BXO (lichen sclerosis) | \ | |
| → fibroepithelial polyps of Pinkus | } | SCC |
| → Cutaneous horn | / | |
| → Pseudoepitheliomatous micaceous and keratotic balanitis | | Verrucous Carcinoma |
| → Condylomata acuminatum (viral-related) | | SCC |
| → Leukoplakia | | SCC & Verrucous Carcinoma |

What are the RFs for melanoma?

- +ve family history
- fair skin
- sun and UV radiation exposure



→ SCC in situ } ERYTHROPLASIA OF QUEYRAT



→ BOWENOID PAPULOSIS



→ SCC of PENIS



→ VERRUCOUS CARCINOMA } BUSCHKE-LOWENSTEIN



→ BCC (vulvar)



→ KAPOSI's SARCOMA





→ PSEUDOEPITHELIOMATOUS MICACEOUS AND KERATOTIC BALANITIS } EXTRA-MAMMARY PAGET'S DISEASE } A – vulva
B – scrotal base



→ CUTANEOUS T-CELL LYMPHOMA } MYCOSIS FUNGOIDES
A – limited plaque stage
B – more advanced plaques, patches, tumours

BENIGN CUTANEOUS DISORDERS SPECIFIC TO MALE GENITALIA

List some benign skin disorders seen **ONLY IN MALE GENITALIA**.

- 1) angiokeratoma of Fordyce
 - benign, vascular ectasias of dermal blood vessels on penis or scrotum
 - 1- to 2-mm red or purple papules +/- generalized scrotal redness
 - **IF FOUND ON PENILE SHAFT, consider Dx of Fabry's disease**
 - Rx → YAG, KTP or argon laser photocoagulation if symptomatic (bleeding)
- 2) pearly penile papules
 - benign, white, dome-shaped, closely spaced small papules on glans penis
 - **acral angiofibromas**
 - often circumferentially arranged at corona
 - very common, especially if uncx'd } 15-50% of post-pubertal M
 - NOT associated with HPV or cervical CIN
 - Rx → cosmetic treatment only with CO2 laser or cryotherapy
- 3) Zoon's balanitis
 - **aka plasma cell balanitis**
 - smooth, moist, erythematous, well-circumscribed plaques on glans +/- shallow erosions
 - occurs in **uncx'd men**
 - **must r/o SCC & extra-mammary Paget's disease**
 - Rx → Cx
 - topical steroids or laser therapy for symptom relief if Cx not wanted
- 4) Sclerosing lymphangitis
 - nonvenereal sclerosing lymphangitis **associated with vigorous sexual activity**
 - indurated, slightly tender cord involving sulcus & adjacent penile skin
 - Rx → self limiting (several wks)
 - reduce vigorous sex
- 5) median raphe cyst
 - found on ventral aspect of penis, most commonly near glans
 - don't communicate with urethra
 - Rx → surgical removal
- 6) ectopic sebaceous glands
 - found on penile shaft



→ ZOON'S BALANITIS



→ ANGIOKERATOMA OF FORDYCE

COMMON MISCELLANEOUS CUTANEOUS DISORDERS

What are some other common genital skin lesions?

- 1) skin tags } soft, skin-coloured, pedunculated lesions that are usually asymptomatic
} common & found anywhere on the body } seen in 50% of people
→ r/o multiple fibrofolliculomas (hamartomatous skin lesion) associated with Birt-Hogg-Dube syndrome
- 2) epidermoid cysts } **most common cutaneous cysts**
→ common on scrotum
} usually asymptomatic but can rupture or get superinfection
} may get dystrophic calcification, a cause of **scrotal calcinosis**
Rx → excision
→ if superinfection, may need I&D +/- ABx
- 3) seborrheic keratosis } brown macules, plaques, and papules with variable pigmentation
→ if acute increase in number must r/o internal malignancy
} very common with increasing frequency with age
→ **found anywhere except palms, soles, mucous membranes**
} waxy “stuck-on” appearance
} **must r/o melanoma & warts and may be assoc’d w/ internal Ca**
Rx → cosmetically removed (shave excision or liquid nitrogen)
- 4) Lentigo Simplex } brown-pigmented macules NOT related to sun-exposure
} found anywhere on body, including nails & mucous membranes
→ in genitalia, common on labia, vaginal introitus, perineum, & glans penis
} **if multiple lesions + intestinal polyps, must r/o Peutz-Jeghers**
Rx → Bx if atypical shape or color suspicious for malignancy
- 5) mole (nevus) } slightly altered melanocytes arranged in a cluster
} named by location
→ junctional
→ intradermal
→ compound
Rx → Bx to r/o malignancy if any atypical features
- 6) dermatofibroma } small hyperpigmented nodules
} spindle-shaped fibroblasts & myofibroblasts
} “dimple sign” → downward movement upon pinching lesion
- 7) neurofibroma } neuromesenchymal tissue with residual nerve axons
} found anywhere on the body, including labia & scrotum
→ soft, rubbery nodular lesions
→ digital pressure causes invagination (button-holing)
} **if multiple lesions, must r/o neurofibromatosis**
- 8) capillary hemangioma } proliferation of blood vessels
→ majority involute during childhood or early adolescence
- 9) vitiligo } acquired skin depigmentation disorder affecting 0.5-2% of population
} large patches of skin becomes amelanotic with well demarcated borders
→ must r/o lichen sclerosis in genitalia
Rx → topical cosmetics, UV exposure, PUVA therapy, skin grafting

What is Leser-Trelat syndrome?

- acute increase in size & number of seborrheic keratoses
- **associated with internal malignancy**



→ MISCELLANEOUS SKIN LESIONS } A – Lentigo simplex (penile melanosis)
 B – Compound melanocytic nevus
 C – dermatofibroma
 D – seborrheic keratosis
 E – epidermoid cyst
 F – pedunculated neurofibroma
 G – vitiligo

Chapter #14 – TB, Parasitic, and Fungal Infections of the GU System

GU TUBERCULOSIS

How common is TB?

- WHO estimates 1/3 of world is infected with *M. tuberculosis*
- rates of TB have been steadily declining since early 90's
 - was on the rise from mid 80's until early 90's due to AIDS, immigration, etc
- immigrants account for ~50% of TB cases in the US

Describe the ultrastructure of the TB organism.

- **small bacilli with thick wall** separated from membrane by a translucent zone
- no true capsule or flagellum } non-motile
- cell wall is complex structure made of 4 layers
 - peptidoglycan + 3 layers of peptides, polysaccharides, and lipids

What organisms make up the *M. tuberculosis* complex?

- *M. tuberculosis*
- *M. bovis*
- *M. microti*
- *M. africanum*

What is the behaviour of the non-tuberculous mycobacteria?

- rarely cause disease in GU tract
- often resistant to one or more of the 1st line drugs

What is the association of TB and HIV?

- worldwide, **TB is the most common opportunistic infection in AIDS patients**
- probability of developing active TB in HIV +ve patient with previous *M. tuberculosis* is 10% PER YEAR
 - cf 5-10% LIFETIME risk of active TB if HIV –ve and hx of exposure to *M. tuberculosis*
- all HIV +ve patients should undergo TB testing so they can be offered Rx for latent infection
- all patients that contract TB should be offered HIV testing

How is TB transmitted?

- **almost all *M. tuberculosis* infections are acq'd by inhalation of aerosolized droplet nuclei**
- greatest risk of transmission is exposure to a patient with laryngeal or cavitary pulmonary TB
- probability of infection depends on:
 - a) duration of exposure to source case
 - b) size of bacillary inoculum inhaled
 - c) infectivity of *M. tuberculosis* strain
- **up to 50% of the active disease occurs within 2yrs of infection**
 - which is why anti-TB prophylactic meds recommended if evidence of a new infection (conversion to +ve PPD) or very heavy exposure
 - almost all TB + HIV pts will develop active disease unless anti-TB prophylaxis taken
- GU TB is caused by metastatic spread of *M. tuberculosis* through the blood during initial infection
 - **kidney is the first GU organ involved** } can lie dormant in granulomas for yrs
 - other parts of GU tract become involved by direct extension
 - **epididymis is the most common site in genital tract (fallopian tubes in women)**

What determines the development of active TB?

- depends on interaction between pathogen & host immune response
- *M. tuberculosis* evokes both humoral & cellular immune response } cellular response most important
- T lymphocytes are responsible for generating cytokines that then activate macrophages to become more mycobactericidal
- after initial infection, *M. tuberculosis* usually multiplies unchecked until immune response kicks in
- **once macrophages are activated, initial infection is controlled & bacilli become dormant**

What are the RFs for developing active TB after initial infection (reactivation of dormant TB)?

- “SID Activates Dormant TB”
- Steroids
- Immunosuppressive therapy
- DM
- AIDS
- Debilitating disease
- Trauma

How common is GU TB?

- only ~1% of TB patients have the GU tract as the primary site of disease
- only ~20% of TB patients have only extrapulmonary disease
- **5% of those with extrapulmonary TB have GU involvement**

How does GU TB present?

- consider Dx when pt presents w/ vague, long-standing urinary symptoms w/ no obvious cause
 - **LUTS (no dysuria), hematospermia, painful testicular swelling, S/P pain (rare)**
 - **sterile pyuria**
- most patients affected are 20-40yrs of age
- very uncommon in kids (**epididymis most common site**)
- males affected 2x more often

List the potential causes of sterile pyuria

→ INFECTIOUS

- GU TB
- UTI with fastidious organism
- UTI but on ABx
- class 3 chronic prostatitis
- parasitic infections
- Chlamydia urethritis
- viral infection
- appendicitis

→ NON-INFECTIOUS

- stones
- renal papillary necrosis
- GU sarcoidosis
- tumour
- PCKD
- AIN
- post-RADs cystitis
- post-cyclophosphamide cystitis
- interstitial cystitis

TB of the Kidney, Ureter, and Bladder

How does TB of the KUB present?

- painless frequency
- recurrent cystitis
- symptoms are intermittent
- renal or S/P pain is rare and usually means extensive involvement of kidney and bladder
- **sterile pyuria } classic finding, although 20% don't have leukocytes in urine**
- gross hematuria in only 10%, microscopic hematuria in 50%

How does renal TB develop?

- **activation of a prior bloodborne renal infection**
- organism settles in blood vessels close to glomeruli
- **caseating granulomas** develop & consist of **Langhans giant cells** surrounded by **lymphocytes & fibroblasts**

What are the findings/complications of renal TB?

- caseating granulomas
- extensive medullary nephrocalcinosis } can lead to “autonephrectomy”
- papillary necrosis \ **earliest sign is calyceal contour abN’ities due to papillary necrosis**
- calyceal strictures / **(“moth-eaten” calyces)**
- infundibular stenosis
- UPJO
- hike up renal pelvis (“Kerr’s kink”)
- ureteral fibrosis/strictures
- VUR
- fistulae
- HTN

What are the findings of ureteral TB?

→ **fibrosis & stricture formation**

- **UVJ most commonly involved** } **usually intramural portion**
- rarely involves UPJ
- almost never see involvement of the middle third of ureter

What are the findings of bladder TB?

- bullous granulations, TB ulcers (rare and late finding), tubercles (rare, usually around UO)
 - **usually starts around UO** } **“golf-hole” UO**
 - can get whole bladder covered by inflamed, velvety granulations with ulcers
 - healed ulcers have a stellate appearance
- bladder wall fibrosis & contraction } **“thimble bladder”**



→ KUB of LEFT RENAL TB



→ IVP of LEFT RENAL TB } contracted bladder
on L side

TB of the genitals

How does TB of the epididymis & testis present?

- painful, inflamed scrotal swelling } hard to differentiate from acute epididymo-orchitis
- can also present as painless mass } must r/o testis Ca
- hematospermia
- testicular involvement is almost always secondary to infection of epididymis
- infertility due to scarring & obstruction of epididymis or vas

How does TB of the prostate present?

- uncommon
- often found in TURP specimen
- in rare, fulminating cases, disease spreads rapidly and can lead to a perineal sinus

How does TB of the penis & urethra present?

- uncommon
- appears as superficial ulcer of glans } hard to differentiate from penile Ca
- can rarely present as a solid nodule or as cavernositis with ulceration
- in active phase, urethral TB presents with discharge
- urethral strictures

Investigations

What investigations are warranted in a patient suspected of GU TB?

- PPD skin test
- CXR
- sputum for AFB
- U/A
- urine C&S (need special Lowenstein-Jensen medium)
- routine bloods including creatinine and Ca (especially if calcifications)
- GU imaging (CT urography)

What is the definition of a positive PPD TB test (CHART)?

- 1) reaction of ≥ 5 mm of induration
 - HIV +ve patients
 - recent contacts of TB cases
 - fibrotic changes on CXR consistent with prior TB
 - patient with organ Tx and other immunosuppressed pts
- 2) reaction of ≥ 10 mm of induration
 - recent immigrants (<5yrs) from high-risk countries
 - iv drug users
 - **residents/employees of hospitals**, NHs, RHs, jails, homeless shelters, etc
 - TB lab personnel
 - kids <4yrs of age or if exposed to adults at high risk
 - other high risk patients (DM, silicosis, CRF, head and neck Ca, gastrectomy, leukemias, jejunioileal bypass, etc)
- 3) reaction ≥ 15 mm of induration
 - persons with no risk factors for TB

What is the significance of a +ve PPD TB test?

- evidence of infection
- **no indication as to whether active or latent disease**
- can't be sure that it's *M. tuberculosis* but it is far more common than nontuberculous Mycobacterial disease

What investigations are indicated after a +ve PPD TB test?

- urinalysis } RBCs, leukocytes, pH
- urine C&S } takes 6-8 weeks because *M. tuberculosis* is slow growing
 - } can often be negative so need **3-5 morning cultures**
 - } culture on **Lowenstein-Jensen medium to isolate *M. tuberculosis***
 - urine AFB smears are often negative so not helpful
- CXR } r/o old or active pulmonary TB
- spinal xrays } r/o spinal TB (Potts)
- KUB xray } look for renal calcifications
 - } ureteral calcifications rare and usually only if extensive renal calcifications
 - } calcification of bladder and SVs rare, except in advanced disease
- IVP } largely replaced by CT
- **CT urography } equivalent to IVP**
 - } has benefit of identifying extrapulmonary TB**
- cystoscopy +/- Bx } rarely indicated in Dx of GU TB
 - } Bx to r/o malignancy
- retrograde pyelogram } to characterize lower ureteric strictures
 - } also for directed cultures if it's not certain from which side organisms are coming
- percutaneous nephrostogram } if retrograde access not possible
 - } to decompress obstructed system

What are the IVP findings of GU TB?

- Kidney
 - **small, non-functioning kidney w/ nephrocalcinosis (autoNx)**
 - **“moth-eaten” calyx (earliest sign – from papillary necrosis)**
 - **obliterated/occluded calyx**
 - **infundibular stenosis**
 - caliectasis
 - calyceal or parenchymal destruction
 - **renal calcifications**
 - Kerr's kink (hiked up pelvis)
- Ureter
 - **ureteral dilation above a UVJ stricture**
 - rigid fibrotic ureter
 - **multiple ureteric strictures**
 - filling defects
 - ureteric calcifications (intraluminal)
- Bladder/Urethra
 - **“thimble” bladder (small & contracted)**
 - **bladder calcifications**
 - SV calcifications (intraluminal)
 - fistulae } “watering can” perineum

What are the CT findings of GU TB?

- **parenchymal scarring (most common finding – 80%)**
- nephrocalcinosis
- hydrocalycosis
- infundibular stenosis
- UVJO or UPJO
- hydronephrosis or hydroureter (70%)
- string-of-pearls ureter
- thickened walls of collecting system (60%)
- bladder filling defects

What is the pattern of ureteral calcification seen with TB and schistosomiasis?

- 1) TB } **intraluminal (cast of ureter)**
 } thickened + nondilated ureter
- 2) schistosomiasis } mural calcification
 } usually dilated + tortuous

What is the DDX of calcifications overlying the kidneys on plain film?

- tumour
- inflammatory lesions
- nephrocalcinosis (hyperCa, hyperPTH'ism, distal RTA, MSK, etc)
- renal TB
- renal artery aneurysm

Treatment of TB

What are the indications to treat GU tract TB?

- symptoms
- abN urine sediment
- presence of granulomas
- endoscopic or radiologic evidence of infection
- absence of other pathogens
- repeated demonstration of *M. tuberculosis*

List the different anti-tuberculin meds (CHART)

→ 1st LINE

- 1) **Isoniazid (INH)** } inhibits synthesis of mycolic acids in *M. tuberculosis* by affecting
 300mg enzyme **mycolase synthetase**
 OD } highly active against *M. tuberculosis* and is **bactericidal** at higher []'s
 } 70% excreted by kidneys but NO RENAL DOSING required
 } hepatic dosing recommended
 → **hepatotoxicity** in 10-20%
 } can result in **peripheral neuropathy** d.t. enhanced excretion of Vit B6
 → give **vitamin B6 (pyridoxine)** supplements
 } can also cause SLE
- 2) **Rifampin** } Abx isolated from *Streptomyces mediterranei*
 600mg } inhibits **bacterial RNA synthesis (bactericidal)**
 OD } excreted in urine but NO RENAL DOSING required
 } **hepatotoxicity** is major S/E but can also get **myelosuppression, orange urine**
 } ++**drug interactions (steroids, BCP), red-man syndrome, pruritus, flu-like symptoms**
- 3) **Pyrazinamide** } inhibits **fatty acid synthetase I** of *M. tuberculosis* (**bactericidal**)
 } N/V common as is **interstitial nephritis** and **thrombocytopenia**
 } **hepatotoxicity, arthralgia, hyperuricemia**
- 4) **Ethambutol** } inhibits **cell wall synthesis (bacterostatic)**
 15mg/kg } 80% excreted in urine needs **RENAL DOSING**
 OD } can cause **hepatotoxicity, retrobulbar optic neuritis**
 → need routine **visual acuity** checks and **red-green color** checks

→ 2nd LINE

- 5) streptomycin } aminoglycoside isolated from *Streptomyces griseus*
 } interferes w/ protein synthesis by binding to **30s unit of ribosome (bacterocidal)**
 } not active against intracellular mycobacteria
 } **ototoxic** (reversible if stopped early after symptoms), **nephrotoxic**
- 6) cycloserine (seizures, psychiatric disturbances)
- 7) ciprofloxacin
- 8) ethionamide (GI toxicity, hepatotoxicity, hypoT4)

Why does GU TB respond so well to short-course meds?

- 1) fewer bugs involved in renal form than pulmonary form
- 2) high concentrations of meds in urine (INH, rifampin, pyrazinamide, streptomycin)
- 3) INH and rifampin pass freely into renal cavities in high concentrations
- 4) all meds reach good concentrations in KUB & prostate

What is the medical treatment of TB?

- **key is multi-drug Rx** } decreases duration of Rx & reduces likelihood of drug-resistance
- **GU TB treatment** } **INH + rifampin + pyrazinamide + ethambutol + Vit B6 x 6months**
 - give all meds in one dose qHS
 - longer duration if disseminated TB, TB osteomyelitis, and TB meningitis
- 1st line } INH 300mg od
 - } Rifampin 600mg od
 - } Pyrazinamide 2g od
 - } Ethambutol 1g od
- 2nd line meds } streptomycin 1g od
 - } cipro 1.5g od
 - } amikacin 1g od

What are the RFs for multi-drug resistant (MDR) TB?

- prior Rx
 - living in country with known high MDR TB rates (India, Russia, Dominican)
- Rx → 18-24 months } based on sensitivities

What are the surgical management options for GU TB?

- adjuvant to medical Rx for GU TB
- **if surgery necessary, delay until administration of meds for at least 4-6 weeks**
- aim is organ preservation & reconstruction not just excision
- 1) **Nephrectomy**
 - **indications include:**
 - a) extensive disease involving entire kidney + HTN + UPJO
 - b) co-existing RCC
 - c) symptomatic non-functioning kidney
- 2) **Partial Nx**
 - **rarely indicated** } meds usually control local lesions (hard to justify w/o calcification)
 - **indications include:**
 - a) localized polar lesion w/ calcifications that fails to respond to 6wks of meds
 - b) area of calcification that slowly increases in size, threatening entire kidney
- 3) **Abscess drainage**
 - can all be done percutaneously } no need for open drainage with current imaging
- 4) **Epididymectomy**
 - **indications include:**
 - a) caseating abscess that is not responding to meds
 - b) firm swelling that is slowly growing in size despite meds
 - testicular atrophy can occur in ~5%
 - involvement of testis uncommon and orchiectomy only required in ~5%

What is the management of ureteral strictures secondary to TB?

- **UVJ most common site**
- distal ureter involved in ~10%
- double J stent or NT for drainage of kidney
- start meds
- if deterioration or no improvement after ~3wks, then some advocate steroids
- if deterioration or no improvement after 6weeks, then may need surgical repair of stricture
- method of repair depends on location & degree of stricture } reimplant, Psoas hitch, Boari, etc
- endoscopic treatment have much lower success rates
- recurrence is common, so careful f/u is required

What are the indications for augmentation cystoplasty for GU TB?

- 1) intolerable frequency + pain, urgency, and hematuria
 - 2) capacity <100cc
 - 3) deterioration of renal function
- can use ileum, stomach, or colon
→ minimum CrCl of 15 mL/min
→ inflammation of bladder not contraindication
→ consider low dose ABx for several months post-op

What are the indications for urinary conduit diversion for GU TB?

- 1) hx of psychiatric illness or mental retardation
 - 2) enuresis not related to small bladder capacity
 - 3) intolerable diurnal symptoms with incontinence that has not responded to meds
- can use ileum or colon

Why is routine BCG vaccination not used in developed countries?

- lasts for only 15yrs
- a proportion of patients will have been previously infected
- chance of complications such as lymphadenitis, lupus vulgaris, and “BCG-itis”
- vaccine doesn’t decrease incidence of infection

What is intravesical BCG?

- introduced by Morales 1976
- **attenuated bacillus from *M. bovis* strain**
- induces cellular immune reaction
- decreases recurrence rate & progression of CIS and superficial TCC of bladder

What are the common side effects of intravesical BCG therapy?

- 60-80% get cystitis
- 5% develop serious infection

How do major reactions present after BCG?

→ can develop early (weeks later) or late (months)

- 1) early
 - sensitization by ongoing therapy
 - high fever
 - generalized symptoms (malaise, sweats, etc)
 - systemic infection (most commonly pneumonitis and hepatitis)
- 2) late
 - reactivation of BCG infection
 - characterized by more organ-specific, localized disease
 - GU
 - vertebral
 - vascular tree

Rx → stop BCG
→ anti-TB meds

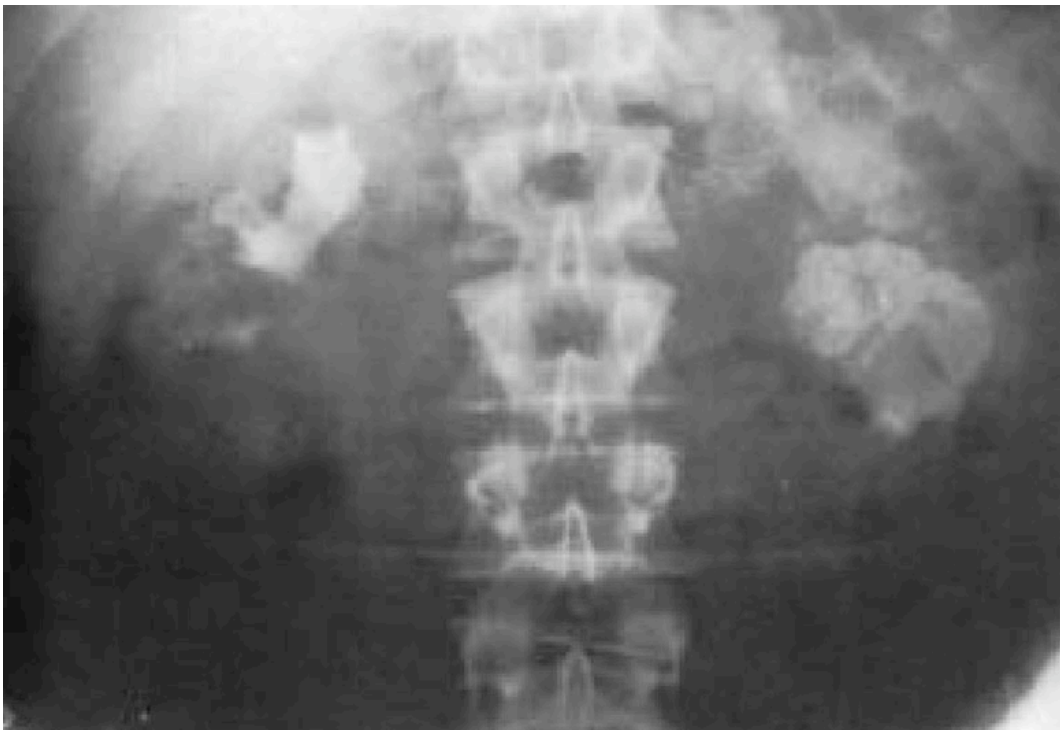
What is BCG sepsis?

- uncommon but can be fatal
- characterized by high fevers, rigors, and hypoTN
- can mimic gram negative sepsis
- can develop DIC, respiratory failure, etc

Rx → anti-TB meds
→ supportive therapy

What is the management of BCG toxicity (Cleveland Clinic protocol)?

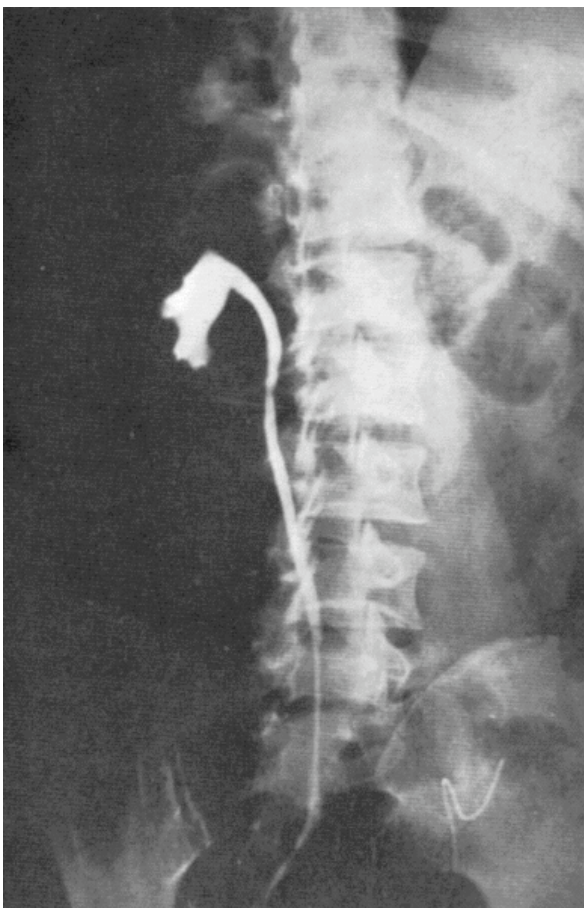
- grade 1 } moderate symptoms <48hrs → mild/moderate irritative symptoms
 - mild hematuria
 - fever <38.5Rx → possible urine C&S to r/o infection
 - symptom management with anticholinergics, pyridium, NSAIDs
 - grade 2 } severe symptoms and/or >48hrs → severe irritative symptoms
 - hematuria
 - fever >38.5Rx → same for grade 1 PLUS;
 - urine C&S, CXR, LFTs
 - ID consult
 - INH 300mg od + rifampin 600mg od until symptoms resolve
 - dose reduction when instillations resume (1/2 to 1/3 dosing)
 - grade 3 } serious complications → hemodynamic changes, persistent high-grade fever
 - } allergic reactions → joint pain, rashRx → same for grade 1 and 2 PLUS;
 - INH 300mg od + rifampin 600mg od for 3-6 months - } solid organ involvement → epididymitis, liver, lung, kidney, osteomyelitis, prostate
- Rx → same for grade 1 and 2 PLUS;
- **INH 300mg od + rifampin 600mg od + ethambutol 15mg/kg od x 3-6mos**
 - **BCG resistant to pyrazinamide so no role**
 - **cycloserine causes severe psych symptoms so not recommended**
 - **consider prednisone 40mg od when response is inadequate or septic shock (NEVER GIVE ALONE)**
 - **vitamin B6 (pyridoxine) supplementation**



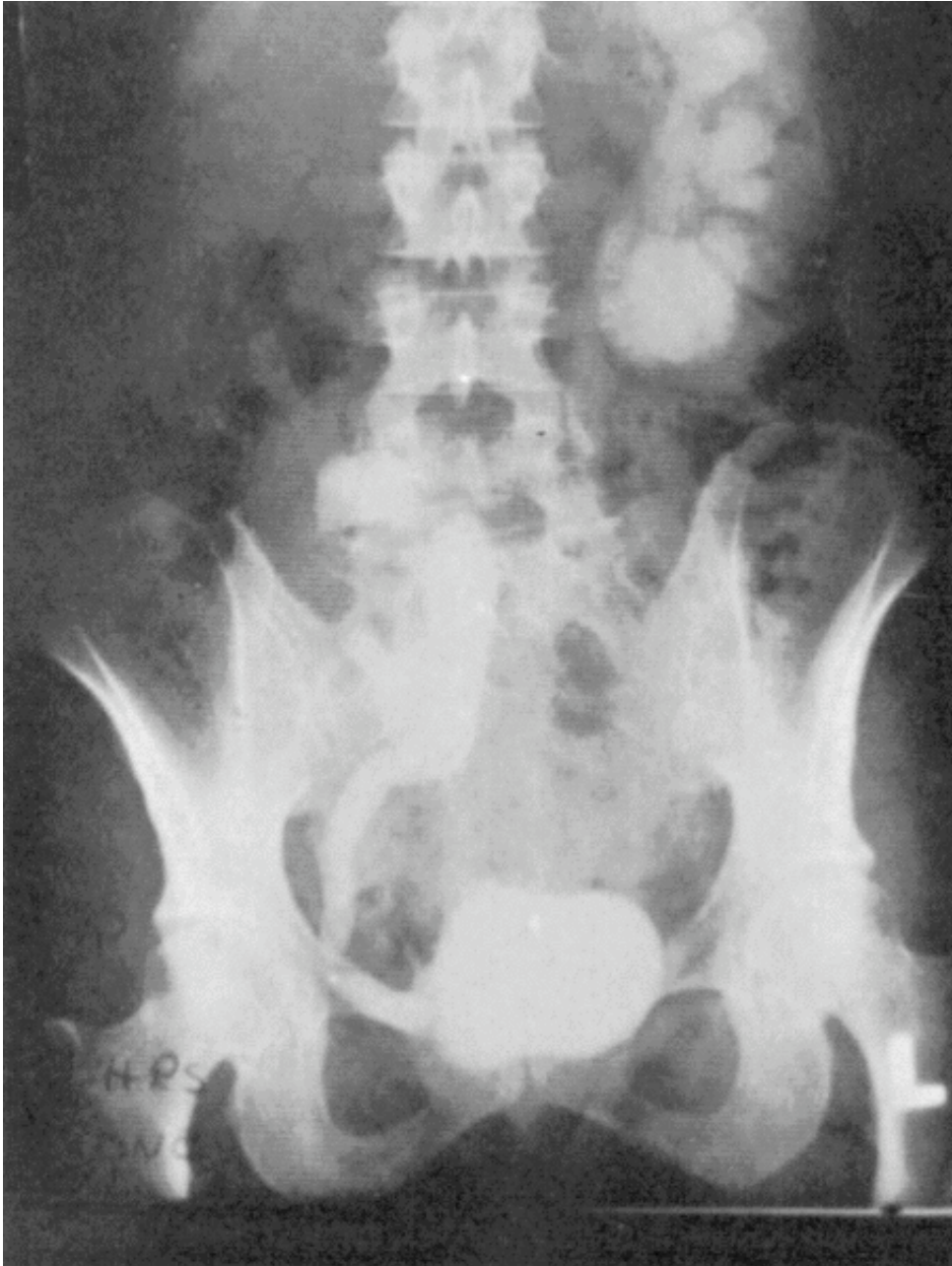
→ RENAL TB } CALCIFICATIONS



→ RENAL TB } DISTORTED CALYCES



→ RENAL TB } OCCLUDED CALYX



→ GU TB } THIMBLE BLADDER (with R VUR)

PARASITIC INFECTIONS

Schistosomiasis

What is Schistosomiasis?

- chronic disease caused by schistosomes, a genus of digenetic **parasitic trematodes**
- **disease results directly from granulomatous host response to schistosome eggs**
 - T cell dependent
- *S. haematobium* is responsible for GU schistosomiasis
 - can differentiate *S. haematobium* from other bugs by looking for **eggs with terminal spines (others have lateral spines)**
- common in Middle East and Africa (Lake Malawi)
- can cause disease in other parts of body such as the GI tract (*S. mansoni* and *S. japonicum*)

What is the life cycle of the *S. haematobium*?

→ “**Malawi Snails Cause Schisto**” } Miracidia in Lake Malawi enters Snail and becomes Sporocysts, then release into water as Cercariae, then enter humans & become **Schistosomulum**

1) asexual reproduction

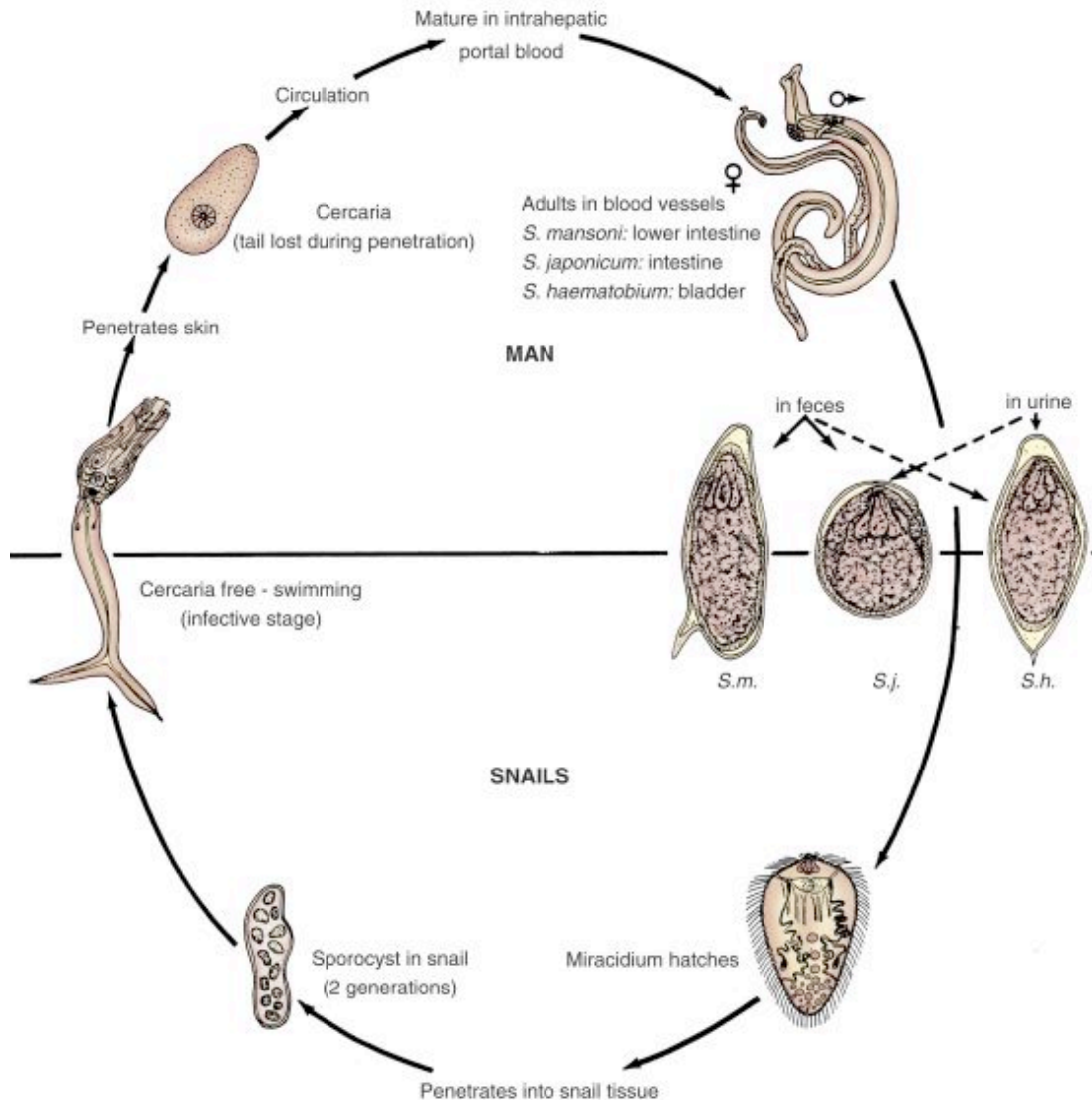
- miracidia enters snail of *Bulinus* species and transforms into **sporocysts**
- sporocysts produce 20-40 daughter sporocysts, each making 200-400 cercariae
- cercariae leave daughter sporocysts, migrate to snail surface, and emerge into fresh water
- **cercariae** penetrate unbroken skin of humans and sheds its tail to become a schistosomulum
 - if cercariae don't penetrate skin within a few hrs, they die
- **schistosomulum** congregate in lung for 4-7 days, in liver from 2nd week onward
 - adult worms do not produce significant disease in host
 - adults pair off and go to different sites to lay eggs

2) sexual reproduction

- adult worm (1.5cm) **resides in vesical & pelvic venules**
- M & F worms pair and attach to endothelium of blood vessels
- **lays eggs in venules**
 - single worm pair can spawn 250,000 to 600,000 eggs during lifespan
 - 20% of eggs cross into hollow viscera and is excreted into urine or feces
 - some eggs can travel in bloodstream to lungs, liver, etc
 - rest of eggs remain entrapped and become calcified and accumulate
- estimated life span of worm is 3-6yrs
- egg matures for several days until the **miracidium forms**
 - if mature miracidium doesn't get released into water, they die and egg degenerates
- if miracidia exposed to water (urine or feces) then they migrate in fresh water to penetrate snail
- in active infection, all egg stages are seen
- in cured or inactive infection, only degenerated (dark) or calcified eggs are seen

Describe the pattern of oviposition in schistosomiasis.

- worm pairs distributed widely in pelvic & mesenteric venous plexuses
 - **egg laying only occurs in pelvic lower urinary tract**
- deposits eggs in groups not singly
 - get composite granulomas not unioval granulomas



→ LIFE CYCLE OF A SCHISTOSOME } “Malawi Snails Cause Schisto”

Describe the bladder pathology in schistosomiasis.

- active urinary schistosomiasis
 - viable adult worm pairs, sustained egg laying, and vigorous granulomatous host response
 - perioval granulomatous inflammation } may be filled w/ viable eggs
 - bulky hyperemic polypoid masses projecting into lumen
- inactive urinary schistosomiasis
 - occurs after adults worms have died
 - absence of viable worms in tissue/urine
 - presence of sandy patches } flat, tan mucosal lesions of various depth
 - made of calcified eggs in dense fibrous tissue matrix
 - **calcified bladder on x-ray (“Baby’s head”)**

What are the different patterns of egg accumulation in schistosomiasis?

- 1) apicentric } begins and persists at dome
- 2) basocentric } begins at base and trigone
- 3) combined } randomly dispersed b/w based and apex

What are the clinical stages of schistosomiasis?

- 1) **swimmer's itch (schistosomal dermatitis)**
 - pruritic macular rash at site of cercarial penetration } 3-18 hrs after exposure
- 2) **acute schistosomiasis (aka Katayama fever)**
 - fever, lymphadenopathy, splenomegaly, eosinophilia, urticaria & other manifestations of serum sickness-like disease
 - occurs 3-9 weeks after infection
 - more common with *S. japonicum* } rare with *S. haematobium*
- 3) **chronic urinary schistosomiasis**
 - much more common than acute disease
 - a) **chronic active phase**
 - eggs deposited in tissue, traverse bladder and excreted
 - **hematuria + terminal dysuria**
 - enters quiescent period } sx decrease, egg deposition occurs at lower rate
 - **silent obstructive uropathy occurs** } hydronephrosis
 - **calcifications throughout collecting system**
 - chronic/recurrent UTI w/ Salmonella
 - intermittent fever, anemia, splenomegaly
 - nephrotic syndrome
 - b) **chronic inactive phase**
 - viable eggs no longer detected in urine
 - **"sandy patches" present** } flat, tan mucosal lesions of various depth
 - fibrosis & symptoms due to obstructive uropathy
 - **calcified bladder ("fetal head")**

How can one make the Dx of schistosomiasis?

- 1) **hx** } **"Where have you been?"**
- 2) **urine** } presence of **terminally spined eggs**
 - egg excretion peaks b/w 10am-2pm
- 3) **rectal or bladder mucosal bx** } eggs seen on squash prep
- 4) serologic testing
- 5) radiologic testing } most important in chronic inactive schistosomiasis
 - Xray } calcified bladder (looks like fetal head), striations in ureters and renal pelvis
 - ureteral calcifications are mural (unlike TB – forms cast of nondilated ureter)
 - IVP } hydronephrosis, nonfunctioning kidney, ureteral stenosis, bladder & ureteral filling defects
 - mural calcification, tortuous ureters
 - VCUG } presence of VUR (occurs in 25%)
 - US } thickening of bladder wall, polypoid lesions of GU tract, hydro, calcific sandy patches
 - CT } obstructive uropathy and calcific lesions

What is the medical management of schistosomiasis?

- 1) **praziquantel**
 - interferes w/ ion transport in schistosome tegument
 - **drug of choice** } works against all schistosomal species
 - 40mg/kg PO x 2 doses
 - S/E's } GI complaints, h/a, dizziness, fever
- 2) **oxamniquine**
 - effective only against *S. mansoni*
 - given over 2-3 days

What are the indications for surgical treatment of schistosomiasis?

- always treat with meds first
- 1) complications that have not responded to medical treatment (eg obstructive uropathy)
- 2) intractable bladder hemorrhage

What is the prognosis of pts w/ schistosomiasis?

- generally good } determined by overall intensity and risk of reinfection
- pts that die are usually young, early stage disease, and heavy total egg burden
- prognosis good w/ newer drugs
- poor prognosis w/ bacterial superinfection
- transplant donor/recipient not contraindicated } need 2 months of chemo prior

How can one prevent infection w/ schistosomiasis?

- **no effective prophylactic drug**
- avoid infected streams, rivers, ponds, lakes

What are the anatomic GU complications of *S. haematobium* infection?

1) Kidney and Ureter

- **stones**
- ureteritis cystica calcinosa
- **hydroureteronephrosis } due to obstruction and ureteral hypotonia**
 - hydroureter usually occurs before hydronephrosis
 - hydronephrosis is final stage
- ureteral obstruction
 - occurs at UO, interstitial ureter, juxtavesical ureter, and/or lower 1/3 ureter
 - most often caused by concentric/hemiconcentric polypoid lesions in interstitial and adjacent extravascular ureter
 - eggs perforate urothelium } allow urine into interstitium, causing spasm
 - ureteral hypotonia occurs
- Rx → ureteric Sx if residual disease after meds
- **renal failure (SOU – schistosomal obstructive uropathy)**
 - **most common sequelae of GU schistosomiasis**
- XGP

2) Bladder

- polyposis
- **sandy patches**
- **"contracted bladder" syndrome**
 - usually occurs in later chronic active stage, when egg burdens are highest
 - get constant deep lower abdo/pelvic pain, LUTS, UI
- ulceration
 - 2 types } acute (necrotic polyp sloughs) or chronic
 - occurs at posterior midsagittal line middle to upper
- Rx → chronic deep bladder ulcers requires partial cystectomy (not fulguration)
- hyperplasia/metaplasia
 - squamous or adenomatoid differentiation
 - epidermization
- cancer } SCC and adenocarcinoma
 - early onset (40-50 yrs), high frequency of SCC (60-90%)
 - SOU predisposes to UTI w/ bacteria that produce carcinogenic nitrosamines
 - usually on posterior or lateral wall
 - 40% well-differentiated: good prognosis
 - nocturia, pain, hemorrhage
- Rx → Radical anterior exenteration w/ urinary diversion
- UO obstruction
- UTI
 - bacteria produce carcinogenic nitrosamines
 - recurrent UTI from *Salmonella*

3) Urethra, Prostate, SV, BOO, Genitals

- cervical stenosis } schistosomal cervicitis & vaginitis (dyspareunia common)
- asymptomatic hematospermia
 - eggs/blood in ejaculate
 - **no documented case of fetal schistosomiasis**

What are the anatomic non-GU complications of *S. haematobium* infection?

- GI tract
 - sandy patches in rectum
 - schistosomal colonic polyposis
 - abdo pain, dysentery, finger clubbing, arthralgia, anemia, protein-losing enteropathy
 - requires cross-infection w/ *S. haematobium* and *S. mansoni*
 - schistosomal appendicitis
- pulmonary involvement
- CNS involvement
 - space-occupying lesion, myelitis, transverse myelitis
- bilharziomas

What are the different types of hydroureter seen in schistosomiasis?

- 1) segmental (25%)
 - involves lower ureter
 - rarely any significant hydronephrosis
- 2) tonic (25-30%)
 - dilated tortuous thick-walled trabeculated ureter w/ marked hypertrophy & active peristalsis
 - involves entire ureter proximal to an obstructive lesion
 - get significant hydronephrosis
- 3) atonic (35%)
 - dilated tortuous thin-walled ureter w/o peristalsis and atrophic fibrotic ureteral muscle
 - involves entire ureter proximal to an obstruction

Filariasis

What is the etiologic agent in genital filariasis?

- 1) Lymphatic filariasis
 - ***Wucheria bancrofti***
 - causes 90% of lymphatic filariasis in humans
 - *Brugia malayi*
 - *Brugia timori*
- 2) Non-lymphatic filariasis
 - *Loa*
 - *Dietalonnema*
 - *Dirofilaria*
 - *Mansonella*
 - *Onchocerca volvulus*: causes scrotal elephantiasis, African river blindness

Describe the life cycle of the lymphatic filariae.

- cycle proceeds from **human to mosquito and back**
- Mosquito
 - female mosquito ingests microfilariae (first-stage larvae) in blood meal
 - larvae become infective and then go to mosquito salivary glands
 - on next bite, infective larvae deposited on skin and penetrate mosquito bite
- Human
 - larvae proceed to larger lymphatic vessels
 - *W. bancrofti* adult filariae live in periaortic, iliac, inguinal, and intrascrotal lymphatics
 - female lays eggs

Where is the distribution of lymphatic filariae?

- distributed in tropics and subtropics

Describe the pathogenesis of lymphatic filariasis.

- 1) Prepatent period
 - **lymph vessels harbour worms → dilated**
 - edema, vasodilation, inflammatory infiltration of tissues drained by lymphatics
- 2) Early established infection
 - **lesions persist and cause significant scarring**
 - lesions at worms' nesting areas } epididymitis, orchitis, filarial lymphangitis, filarial abscess
 - worm death causes inflammatory response
 - exudative filarial lesions simulate abscesses → sterile
- 3) Late infection
 - **lymph vessels obstructed**
 - huge hydroceles and scrotal and penile elephantiasis
 - elephant scrotum often becomes secondarily infected, BUT hydroceles don't

What are the various forms of clinical lymphatic filariasis?

- 1) asymptomatic
 - skin test reactivity only } no microfilaremia, no clinical evidence of disease
- 2) filarial fevers
 - episodic fevers, lymphangitis, epididymitis, transient edema, small hydroceles
 - typically amicrofilaremic
 - chronic hydrocele, chyluria, lymphedema, lymph scrotum
- 3) chronic lesions
 - **funiculoepididymitis**
 - pain, lumpy or cordlike swelling, hydrocele
 - varicocele or thrombosis of pampiniform plexus
 - Rx → ABx, surgical decompression or excision of filarial nodules, orchiectomy
 - orchitis is rare, sterility is rare
 - **hydrocele**
 - thick fibrous tunica w/ cholesterol or Ca deposits
 - calcification so rare in hydrocele, that presence suggests infectious/filariasis
 - milky or sediment-rich hydrocele fluid
 - **scrotal and penile elephantiasis and lymph scrotum**
 - skin ulcers and sepsis
 - Rx → excision w/ grafting
 - **chyluria**
 - dying worms cause lymphatic obstruction
 - rupture of lymphatic varix into collecting system
 - severe protein loss, hypoalbuminemia, anasarca
- 4) tropical eosinophilia
 - sustained peripheral eosinophilia
 - responds to antifilarial drugs

How does one make a Dx of filariasis?

- 1) **histologic finding of adult worms**
- 2) *Brugia* or *Wucheria* in blood, chylous urine, or hydrocele fluid } peak microfilaremia at midnight
- 3) U/S observation of worms } "filarial dance sign"

What is the medical management of filariasis?

- 1) **diethylcarbamazine (DEC) } 2 mg/kg/day PO TID x 2 weeks (gold standard)**
 - S/E's } fever, N/V, h/a, arthralgias (due to dying filariae)
 - can be used prophylactically } annual dose of 6mg/kg
- 2) ivermectin } single dose 200-400 ug/kg
 - } no effect on adult filariae
- 3) **albendazole** } kills both adults and microfilariae
- 4) elastic stockings & elevation of extremities
- 5) lymphangiogram + sclerosis of lymphatic fistulae

Other GU Parasites

What is the disease caused by *Onchocerca volvulus*?

→ African river blindness

- transmitted by black flies of *Simulium* species
- blindness + atrophic dermatitis
- may produce scrotal elephantiasis

Rx → ivermectin

- don't use DEC due to severe allergic immune responses to dying microfilariae (Mazzotti reaction)

→ can add 6wk course of doxycycline

What is the disease caused by *Enterobius vermicularis*?

- common intestinal pinworm
- can cause pelvic enterobiasis by migrating up from anus into vagina, into peritoneal cavity

Rx → pyrantel pamoate, mebendazole, or albendazole

What is the etiologic agent of hydatid disease?

→ *Echinococcus granulosus* } larval form is the hydatid

- definitive host } dog
- intermediate host } sheep

How do humans get hydatid disease?

- occurs in **sheep-herding areas**
- accidentally eating eggs excreted in dog feces

How does hydatid disease present?

→ any organ or body part can be involved with hydatid cysts

→ renal hydatids occur in only ~2% of cases of hydatid disease

- pressure symptoms or flank pain } due to slow growth of hydatid cysts over years
- microscopic hematuria (rare)

What are the radiologic findings in hydatid disease?

- thick-walled fluid-filled spherical cyst
→ has **calcified cyst wall +/- daughter cysts**

How does one make the Dx of hydatid disease?

- imaging
- serologic testing

What is the treatment of hydatid disease?

→ Medical

- **albendazole** 400mg PO BID x 1-6 months
- **praziquantel** preoperatively

→ Surgical

- cyst removal if symptomatic } material extremely antigenic
- } **rupture of cysts may cause anaphylaxis**

What is the disease caused by *E. histolytica*?

→ **amebiasis**

- rare cause of renal abscess } R kidney more common
- usually accompanied by liver abscess
- hematuria
- amebic ulceration of perineum

Rx → metronidazole ASAP

FUNGAL INFECTIONS

How can one classify fungal infections of the GU system?

- 1) Opportunistic fungi
 - **Candida } most common**
 - *Torulopsis glabrata*
 - Aspergillosis
 - Cryptococcosis
 - Phycomycosis (Mucormycosis, Zygomycosis)
- 2) Primary fungal infections
 - Blastomycosis
 - Coccidiomycosis
 - Histoplasmosis
- 3) Rare and unusual
 - Phaeohyphomycosis - *Pseudallescheria boydii*
 - *Fusarium* - Rhinosporidiosis
 - Paracoccidioidomycosis - Sporotrichosis
 - Penicillium - Tinea
 - Trichosporon
- 4) Actinomycetes

List the RFs for fungal infections

Candiduria	Ascending infx	Pyelo	Ped Pyelo
- general RFs as for other UTI; RFs are mostly host-related	1) Foley	1) candidal cystitis	1) umbilical artery catheter
1) Foley (80%)	2) DM	2) ileal conduits	2) prematurity
2) surgery (50%)	3) immunosupp.	3) chronic NGB	3) low birth weight
3) DM (40%)	4) obstruction	4) renal pelvic lithiasis	
4) urinary tract disease (40%)		5) obstructive uropathy	
5) cancer (20%)			
6) malnutrition (20%)			
Renal abscess	Fungemia	Vulvovaginitis	
1) DM	1) iv catheters (65%)	1) antibiotics	
2) surgery	2) antibx (100%)	2) BCP	
3) renal transplantation	3) Foley (100%)	3) DM	
4) prolonged abx	4) surgery (70%)	4) pregnancy	
	5) GU surgery (5%)		

Candida

What species of Candida usually cause GU infections?

- **C. albicans: 74%**
- *C. glabrata*: 8% (aka *Torulopsis*)
- *C. parapsilosis*: 7%
- *C. tropicalis*: 3%
- *C. lusitaniae*: 2% → some strains resistant to amphotericin B

What are the primary sites of candidemia infection?

- **intravascular catheters (65%)**
- TPN (42%)
- GU tract (11%) } kidney is a major target organ associated with candidemia
- GI tract (8%)
- respiratory tract (7%)

What are the RFs for *C. albicans* UTI?

→ “CANDIDA SMC”

- Catheterized
- ABx
- Neurogenic bladder
- DM
- Impaired urine flow
- Diversion (ileal conduit)
- Anomalous GU tract
- Steroids
- Malnutrition
- Cancer

What is the presentation of candiduria?

→ usually asymptomatic

- LUTS
- flank pain/renal colic } fungus balls
- pyelo symptoms } flank pain, renal tenderness, fever
- oliguria/anuria } due to obstruction
- recurrent fever in immunocompromised pt

How can one Dx *Candida* infection?

- superficial infection } identification of fungus by smear or culture of wound exudate
- microscopic detection of *Candida* in vaginal exudates or by culture
- bladder } cysto shows white patches on bladder wall + areas of mucosal edema & erythema, and hyphae in exudates
- upper tract } finding fungus in urine, imaging studies (US, IVP, CT) that documents obstruction

What are the various manifestations of candiduria?

- 1) superficial infection
 - around ileostomies/cutaneous pyelostomies
 - post-op wound infection } erythema and pustules in incision sitesRx → topical antifungals
- 2) vaginitis
 - yellowish-white vaginal D/C & gray-white pseudomembranous exudate in vagina
 - pruritis
 - more common in pregnancy or on OCPRx → oral fluconazole (150mg od x1 ... just as good as intravaginal Rx)
- 3) genital infection
 - emphysematous cellulitis
 - epididymitis
- 4) bladder/prostate infection
 - emphysematous cystitis
 - fungal bezoar
 - emphysematous cystitis/prostatitis
 - prostatic abscess
- 5) upper tract infection
 - fungus balls } ureteral obstruction or renal pelvis obstruction
 - candidal pyocalix
 - perinephric abscess } fever, flank pain, +ve culture for *Candida*, abnormal US/CT
 } mainly in DM on prolonged ABx
 - pyelo
 - papillary necrosis
- 6) systemic candidal infection

What is the management of Candidal vaginitis?

- send vaginal exudate for culture/microscopy
- **PO fluconazole 150mg x 1 } as effective as intravaginal clotrimazole**
- nystatin intravaginally x 14 days
- topical imidazoles } butoconazole, clotrimazole, miconazole, terconazole, tioconazole
- boric acid powder 600mg in gelcap intravaginally x 2/52
- chronic infections } ketoconazole 400mg OD x 14d followed by 100mg OD x 6/12

What are the RFs for Candidal pyelonephritis?

- 1) candidal cystitis
- 2) ileal conduit
- 3) chronic neurogenic bladder

What are the RFs for development of renal candidal infection in infants?

- IV catheters
- broad-spectrum ABx
- prematurity
- low birth weight

What is the management of Candidal infection of the upper tracts?

- identify fungus in urine
- imaging studies to document obstructive uropathy } US, IVP, CT → r/o fungus ball
- NT
- IV amphotericin B
- irrigation of renal pelvis w/ amphotericin B
- surgical drainage or Nx for perinephric abscess

What are the predisposing factors to candidemia in the surgical pt?

- renal failure
 - hepatic dysfunction
 - post-op shock
 - ARDS
- fungemia = failure of host resistance
- very ill pts should receive prophylactic antifungals

How can one Dx GU tract Candidal infections?

→ Urine studies

- microscopic examination } budding forms or pseudohyphae
 } pyuria and hematuria
 } fungal casts
- culture from urine } CLED (cystine lactose electrolyte deficient) agar, blood agar,
 and Sabouraud's agar w/ dextrose
- urinary candidal colony counts } high counts if renal infection vs. colonization
 ➔ cannot be used to differentiate colonization from local or invasive
 infection, especially if indwelling catheter

→ Blood/serologic studies

- no lab studies can indicate upper tract infection
- persistence of positive Candida blood cultures
- antibody response to candidal antigen } whole-cell agglutination, agar cell diffusion, latex agglutination, counterimmune electrophoresis, RIAs
- PCR efficacious for detection of occult candidemia

→ Imaging

- cystogram, IVP, retrograde } filling defects
- US } demonstration of fungal material
- CT } mass lesion w/ less attenuation than stone

What are the indications for systemic antifungal therapy?

- symptomatic patients
- very low birth wt infants
- renal Tx
- GU instrumentation

What are the treatment options for a GU candidal infection?

- observation
- general measures } removal of foreign bodies (catheters, IVs)
 } improve nutritional status
 } stop unnecessary antibacterial agents } restore N flora
 } relief of obstruction
 } urine alkalization can decrease multiplication of fungal elements
- antifungals } irrigation (amphotericin B or miconazole)
 → acidic urine decreases effectiveness
 } systemic Tx (amphotericin B or fluconazole) if:
 - local infection
 - invasive or disseminated infection
- surgical } debridement
 } removal of fungal ball
 } correction of underlying abnormalities

Describe the treatment algorithm for a GU candidal infection.

- 1) Initial candiduria } single +ve culture
 - observation if urine colony counts <10000,
 - institute general measures } remove or change catheter (if present)
 } stop antibacterial antibiotics
 } **improve nutritional status**
 } relieve obstruction if present
- 2) if +ve on reculture
 - assess for upper tract abnormalities } US, IVP, CT
 - **if +ve filling defects } perform culture ureteral/renal urine**
 } if +ve:
 - **antifungal irrigation** w/ ampho B via NT or ureteral catheter
 - perc removal of fungal bezoar
 - **systemic ampho B, IV fluconazole**
- 3) if systemic manifestations } fever, WBC, other culture sites +ve?
 - systemic ampho B, IV fluconazole
- 4) if no systemic manifestations
 - bladder irrigation w/ ampho B (50mg in 1000cc water/D5W at 1L/day)
 - PO/IV fluconazole
 - if persistent infection } systemic ampho B, IV fluconazole

What are the potential systemic treatments for "local infection?"

- 5-FC > 100mg/kg/day PO
- fluconazole 100mg PO BID x 10d
- amphotericin B: 200-300mg IV daily
- liposomal amphotericin B
- imidazoles (miconazole and ketoconazole) } poorly excreted by kidney, low urine []'s

What species of Candida are sensitive to fluconazole?

- treats all except C. krusei and C. glabrata**

What is the gold standard for treatment of the pt w/ invasive or disseminated fungal infection?

- amphotericin B 6mg/kg

What are the indications for nephrectomy in the setting of fungal infection?

- 1) fungal abscess
- 2) cellulitis
- 3) diffuse parenchymal infection

Torulopsis glabrata

What are the GU manifestations of *Torulopsis glabrata*?

- voiding LUTs
- pyuria
- hematuria
- epididymitis
- pelvic abscess
- fungemia
- perirenal abscess
- upper tract infection (flank pain, fever, WBC)
- upper tract obstruction

Aspergillus

What is aspergillosis?

- major cause of M&M in immunocompromised patients
- causes variety of pulmonary diseases } cavitary aspergillomas, asthma, etc
- extra-pulmonary aspergillosis is uncommon } cutaneous, GU, naso-orbital

What are the most common species of *Aspergillus* that cause GU infection?

- *A. fumigatus*
- *A. terreus*
- *A. flavus*
- *A. niger*

What are the various GU manifestations of Aspergillus infection?

- 1) renal infection
 - renal aspergillomas/pseudotumours → in AIDS pts
 - abscesses
 - fungal vascular occlusion } renal infarcts
 - } papillary necrosis secondary to vascular occlusion
- 2) prostatic infection
 - BOO
- 3) disseminated aspergillus
 - opportunistic infection seen in DM, AIDS, immunosuppression, organ Tx, cancer

What is the treatment of renal aspergillomas?

- IV amphotericin B 1.5g x 3 weeks + PO itraconazole 200 mg PO BID x 3 months
- meds in conjunction w/ surgical tx

How can one Dx Aspergillus infection?

- urine/tissue biopsy } identification w/ methenamine silver or PAS stain of the fungus
- blood cultures } usually -ve
- PCR amplification

What is the treatment of Aspergillus?

- **poor outcomes in invasive aspergillosis** } **mortality rates ~40-90%**
- Medical } **amphotericin B (traditional drug of choice)**
 - } itraconazole
 - } caspofungin
- Surgical } endourologic access (anterograde or retrograde)
 - } irrigation (via NT or ureteral catheter)
 - } lavage and debulking (PCNL or via ureteropyeloscopy)
 - } re-irrigation
 - } renal exploration, pyelotomy
 - } nephrectomy

Cryptococcosis

What fungus causes cryptococcus GU infection?

→ *Cryptococcus neoformans*

What environment predisposes Cryptococcus to grow?

- live in any environment inhabited by **birds** (esp pigeons)
- found in old attics, buildings, and barn lofts

Describe the symptoms of cryptococcus infection.

→ **usually an asymptomatic pulmonary infection**

- may develop into virulent respiratory infection that mimics severe pneumonia, TB, cancer, or other fungal infections
- often self-limiting

What pts are at increased risk of disseminated Cryptococcus infection?

→ **AIDS pts**

What is the primary site of extrapulmonary Cryptococcus infection?

- CNS is primary target of hematogenous spread
→ meningitis, meningoencephalitis, cryptococcoma

How can one Dx Cryptococcal infection?

- identification in urine, CSF, or other fluids } Sabouraud's glucose agar media
- direct examination of infected fluid w/ India ink
- identification in tissue w/ PAS or methenamine silver stain
- latex agglutination tests
- cryptococcal antigen in urine of AIDS pts

What are the various GU manifestations of Cryptococcal infection?

- 1) adrenal infection
- 2) renal infection
 - cryptococcal pyelo
 - Rx → amphotericin B
- 3) prostatic infection
 - lesions vary from small chronic inflammatory changes to large granulomas w/ caseation
 - prostate is a reservoir for cryptococcus in AIDS pts after Rx for cryptococcal meningitis
 - Rx → requires systemic fluconazole
- 4) genital infection
 - epididymitis
 - Rx → orchiectomy + systemic amphotericin B, ketoconazole, fluconazole
 - penile infection } glans ulcer to large exophytic lesion
 - Rx → excisional bx and systemic Rx (amphotericin B or fluconazole)

Mucormycosis (Phycomycosis)

What genera make up the taxonomic family Mucoraceae?

- *Rhizopus*
- *Rhizomucor*
- *Mucor*
- *Absidia*

What are the manifestations of Mucor infection?

- 1) rhinocerebral infection } sinus, pharynx, meninges, brain
- 2) pulmonary infection } associated w/ haem malignancies
- 3) GI infection } in malnourished kids
- 4) renal involvement } high mortality rate if untreated**
- 5) cutaneous infection and inguinal abscesses
- 6) disseminated zygomycosis } may involve pelvic organs

What pt populations are at increased risk for developing disseminated mucormycosis?

- hemodialysis
- pts who receive deferoxamine (iron chelator)

What is the management of renal mucormycosis?

- **Nx + systemic amphotericin B } ~75% survival**

Blastomycoses

Where is the fungus *Blastomycoses dermatitidis* found?

- endemic in basins of the Ohio, Missouri, and Mississippi rivers
- Great Lakes region and Canada
- fungus has a predilection for moist soil w/ a high organic content

What fungus causes North American blastomycosis?

→ *Blastomyces dermatitidis*

What fungus causes of South American blastomycosis?

→ *Paracoccidioides brasiliensis*

What is the natural hx of Blastomycosis infection?

- following inhalation, pulmonary infection may develop
 - often subclinical and self-limiting
- may disseminate by hematogenous or lymphatic route to extrapulmonary sites
 - skin, bones, GU system

What conditions predispose pts to develop Blastomycosis?

- chronic steroid use
- hematologic malignancy
- solid tumour requiring cytotoxic or radiation therapy
- transplant recipient (solid organ or bone marrow)
- HIV +ve
- ESRD
- end-stage liver disease
- pregnancy

What are the GU manifestations of Blastomycosis infection?

→ GU involvement in 15-20% of pts w/ systemic disease

- 1) prostatitis
 - LUTS, retention
 - prostatic abscess
- 2) epididymitis } commonly involved
- 3) adrenal infection
- 4) systemic blastomycosis

How can one Dx Blastomycosis infection?

- CXR changes
- +ve Blastomyces skin test
- identification of fungus in urine, semen, or tissue
 - identify Blastomyces "broad neck" yeast forms in infected tissue
- serologic tests
 - Blastomyces A antigen

What is the treatment of Blastomyces infection?

- Disseminated disease } systemic amphotericin B 1-3g
- Mild/moderate non-meningeal forms } ketoconazole 400mg OD

Coccidioidomycosis

What fungus causes coccidioidomycosis?

→ *Coccidioides immitis*

Describe the natural habitat of coccidioidomycosis.

- indigenous to semiarid regions of Western US, Mexico, and Central and South America
- thrives in soil conditions that are inhibitory to competing organisms
 - high temperature & increased salinity

What population groups are at increased risk of coccidioidomycosis?

- construction workers
 - farmers
 - archaeologists
- \ } those exposed to dust
/

Describe the natural hx and presentation of coccidioidomycosis infection.

- **usually asymptomatic and transient pulmonary infection**
 - more virulent infection in some cases
 - high fever, cough, night sweats, or pleuritic pain
- "allergic" reaction to infection } erythema nodosum
 - aka "**valley bumps**" or "**valley fever**"
- <1% develop extrapulmonary manifestations
 - meninges, bone, skin, joints, soft tissue

What are the RFs for disseminated coccidioidomycosis?

- increased skin pigmentation
- pregnancy
- age < 5 or >65
- steroid use
- chemotherapy
- malignancy
- HIV+/AIDS

What are the GU manifestations of coccidioidomycosis?

- [illegible]

What are the renal radiographic findings of coccidioidomycosis?

- **similar to TB** } "moth-eaten" calyces, infundibular stenosis, renal calcification

How can one Dx coccidioidomycosis?

- History } pt travelled to endemic areas, environmental hazards, immune suppression
- Serologic studies
- Culture draining sinuses
- tissue stains w/ PAS or methenamine silver

What is the treatment of coccidioidomycosis?

- systemic antifungals } amphotericin B 1-1.5 mg/kg/d x 2-3mo
 → lipid formulations (less toxic)
- } fluconazole
- surgical resection of infected scrotal contents or prostate

Histoplasmosis

What fungus causes histoplasmosis?

- *Histoplasmosis capsulatum*
- individuals that work in chicken coops, infested caves, window sills, and other bird areas at higher risk

What is the natural hx of histoplasmosis?

- asymptomatic, self-limiting pulmonary infection } may have cough, fever, hemoptysis
- if not treated, can become chronic pulmonary infection
- disseminated and virulent disease

How can one Dx histoplasmosis?

→ **major opportunistic infection in AIDS patients**

- CXR } small pulmonary granulomas/cavitations and calcification
- +ve histoplasmin skin tests
- identification of *H. capsulatum* in tissue specimens by methenamine silver or Giemsa stain

What are the GU manifestations of histoplasmosis?

- 1) extrapulmonary } liver, spleen, LNs
- 2) adrenal } Addison's disease
- 3) renal
- 4) genital } superficial penile ulcers
 } epididymal histoplasmosis } Rx → surgical excision

What is the treatment of histoplasmosis?

- disseminated histoplasmosis } systemic amphotericin B
- imidazoles, IV miconazole, and PO ketoconazole → not good as primary Rx
- long-term suppression with PO itraconazole to prevent relapse
- immunocompromised pts } IV amphotericin B w/ long-term itraconazole
- removal of infected organ

Sporotrichosis

Describe the natural hx of sporotrichosis.

- fungus gains entry via skin trauma } thorns, animal/insect bites
- induces chronic lymphocutaneous lesion
- dissemination } bones, joints, sinus, meninges

Actinomyces

Describe the urogenital manifestations of actinomyces infection.

- 1) retroperitoneal abscess
- 2) renal infections
- 3) renal-colic fistula
- 4) renal duodenal fistula
- 5) intratesticular abscess
- 6) ureteral obstruction

How can one Dx actinomyces infection?

- identification of sulfur granules in infected tissue
- microcolonies of bacteria } develop yellow pigmentation

What is the treatment of actinomyces infection?

- Medical } **penicillin IV 20 million units / day x 2 weeks**
 - } ampicillin PO 1500mg/day x 4 months
 - } tetracycline, cipro, erythromycin
- Surgical } debridement of all infected tissue

ANTIFUNGALS

Describe the pharmacology of amphotericin B.

- polyene antifungal agent } fungicidal + fungistatic properties
- **binds to ergosterol component of the fungal cell membrane**
 - results in disruption of internal cellular components to cause electrostatic flux
- $T_{1/2} = 15$ days

What are the S/Es of amphotericin B? } } } “AAA MMM PPP HHH O B”

- biliary clearance (usually no renal dosing required)
- lipid formulations just as effective but has less potential for adverse S/Es
- **iv administration can result in rigors, chills, fever**
 - Rx → steroids 20mg IV given w/ amphotericin B
- **Anaphylaxis** } for liposomal amphotericin B
- **Anemia**
- **Arrhythmias**
- **Myalgia/flu-like symptoms** (fever, chills, etc)
- **Multi-organ failure** (liver, etc)
- **Microcephaly** (only congenital anomaly)
- **Pain**
- **Phlebitis**
- **Platelets low** (thrombocytopenia)
- **HypoK**
- **HypoCa**
- **HypoMg**
- **Ototoxicity**
- **Bean toxicity** (nephrotoxicity) } RTA, pyuria, proteinuria, etc → **treatment limiting S/E**

Describe the pharmacology of flucytosine.

- 5-FC is a fluorinated pyrimidine
- converted to 5-FU by cytosine deaminase
- readily absorbed by GI tract
- $T_{1/2} = 3-5\text{hrs}$
- drug excreted unchanged by filtration } can be cleared by dialysis

What are the S/Es of flucytosine?

- GI } N/V/D/enterocolitis
- LFT changes
- Haem } bone marrow depression, anemia, leukemia, thrombocytopenia, aplastic anemia
- headache, confusion
- **drug resistance in 10% of *C. albicans* → limits use in most GU fungal infections**

Describe the pharmacology of the Azoles.

- 1) imidazoles } **inhibits cytochrome P-450**
 - topical } clotrimazole, econazole, miconazole
 - oral } ketoconazole 400mg/day, increase to 800mg/day
 - absorbed from GI tract, peak concentration in 1-4 hrs
 - absorption limited if pt has achlorhydria or uses antacids (cimetidine or ranitidine)
 - **poor renal excretion → low urinary levels**
 - LARGELY REPLACED BY NEWER AZOLES
 - IV } miconazole
- 2) triazoles } **greater affinity for fungal cytochrome P-450 than imidazoles**
 - itraconazole
 - 200mg PO TID x 3d, then 200-400mg OD
 - lipophilic } tissue levels 2-3 times higher than serum levels
 - absorption enhanced if take w/ food
 - less S/Es than ketoconazole
 - works against *Aspergilla*, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Sporotrichosis*
 - fluconazole
 - 200mg PO OD x 7d
 - PO administration not affected by food
 - water soluble } high levels in plasma, CSF, and urine
 - just as effective as bladder irrigations w/ amphotericin B for Rx of bladder candidal infection
 - less S/Es than amphotericin B
 - efficacious in **Rx of *Candida* & *Cryptococcus* (NOT for *C. glabrata*, *C. krusei*)**

What important drug interactions occur involving the azoles & other commonly used meds?

- ↓'d plasma concentration of azole ("ASH falls down")
 - Antacids (ketoconazole, itraconazole)
 - Sucralfate (??ketoconazole)
 - H_2 blockers (ketoconazole, itraconazole)
- Increased plasma concentration of azole ("RIP it up")
 - Rifampin (ketoconazole, itraconazole)
 - INH (ketoconazole)
 - Phenytoin (ketoconazole, itraconazole)
- Increased plasma concentration of coadministered drug ("Pills Will Surge Serum Concentration Dude")
 - Phenytoin (ketoconazole, fluconazole)
 - Warfarin (ketoconazole, itraconazole, fluconazole)
 - Sulfonylurea drugs (esp tolbutamide) (ketoconazole, itraconazole, fluconazole)
 - Statins
 - Cyclosporine (ketoconazole) → **keto increases CsA**
 - Digoxin (itraconazole)

What is caspofungin?

- member of **new class of antifungals called the echinocandins**
- inhibits synthesis of glycan component of fungal cell wall
- **iv dosing only**
- few S/Es
- active against *Candida* and *Aspergillus*
- phenytoin, rifampin, dexamethasone may decrease serum levels of caspofungin

What are the other treatment modalities for fungal infections?

- alkalinization
→ ideal growth pH ranges from 5.1-6.4 (similar to urinary pH)
- allylamine (terbinafine and naftidine) } ergosterol biosynthetic inhibitors w/ antifungal activity
- transfer factor } derived from lymphocyte lysates
- GSF

What are the common or serious adverse effects of systemic antifungals?

Table 22–3. COMMON OR SERIOUS ADVERSE EFFECTS OF SYSTEMIC ANTIFUNGAL DRUGS

Organ or System	Drug					
	<i>Amphotericin B</i>	<i>Flucytosine</i>	<i>Miconazole</i>	<i>Ketoconazole</i>	<i>Fluconazole</i>	<i>Itraconazole</i>
Gastrointestinal tract	Nausea, vomiting, anorexia	Nausea and vomiting (5% of patients), diarrhea, abdominal pain	Nausea and vomiting (<15% of patients)	Nausea and vomiting (<10% of patients), abdominal pain, anorexia	Nausea and vomiting (<5% of patients)	Nausea and vomiting (<10% of patients)
Skin	—	Rash	—	Pruritus, rash	Rash, possibly exfoliative (Stevens-Johnson syndrome)	Pruritus, rash
Liver	—	Asymptomatic rise of plasma ATA (7% of patients), hepatitis (rare)	—	Asymptomatic rise of plasma ATA (2%–10% of patients), hepatitis	Asymptomatic rise of plasma ATA (<1%–7% of patients), hepatitis	Asymptomatic rise of plasma ATA (<1%–5% of patients), hepatitis (rare)
Bone marrow	Anemia	Anemia (less common), leukopenia, thrombocytopenia	Anemia, leukopenia, thrombocytosis or thrombocytopenia	—	—	—
Kidney	Azotemia (80% of patients), renal, tubular acidosis, hypokalemia, hypomagnesemia	—	—	—	—	—
Endocrine system	—	—	Hyperlipidemia, hyponatremia	Adrenal insufficiency (rare), decreased libido, impotence, gynecostasia, menstrual irregularities	—	Hypokalemia, hypertension, edema, impotence
Other	Thrombophlebitis, headache, fever and chills	Confusion, headache	Phlebitis, fever, psychosis	Headache, fever and chills	Headache, seizure	Headache, dizziness

ATA, aminotransferase.

Adapted from Como JA, Dismukes WE: Oral azole drugs as systemic antifungal therapy. *N Engl J Med* 1994;330:263–272. Copyright 1994 Massachusetts Medical Society. All rights reserved.

What are the **side effects of ketoconazole**?

- **gynecomastia**
- lethargy & weakness
- **hepatotoxicity**
- **visual disturbances**
- nausea
- ED
- **adrenal insufficiency**
- increases coumadin levels (inhibits CYP450)
- H/A
- skin rash
- thrombocytopenia
- increased TG's
- osteoporosis

Describe the medical tx (including doses) for each major GU fungal infection (CHART).

- 1) Candida and Torulopsis
 - balanitis } nystatin cream or fluconazole 150mg PO x1
 - vaginitis } nystatin intravaginally x 14d
 - bladder } fluconazole 150mg PO OD x 7d
 - kidney } amphotericin B 1g IV + 40ml/hr irrigation
 - prostate } fluconazole 200mg PO BID x 6 weeks
- 2) Aspergillosis
 - renal or prostate } amphotericin B 1.5mg/kg/day IV + 40ml/hr irrigation x 6-18wk + itraconazole 200mg PO BID x 1yr
- 3) Cryptococcosis
 - prostate } amphotericin B 1-3.4g total dose IV + flucytosine 100-150mg/kg/day x 4-6wk then fluconazole 200-600mg PO OD x 2-6/12
 - epididymis/testis } amphotericin B + consider orchiectomy
- 4) Mucormycosis
 - renal } amphotericin B > 1g IV x 1mo (should consider Nx)
- 5) Blastomycosis
 - prostate } ketoconazole 400mg PO OD x 1mo + amphotericin B 1-3g IV q3/12
 - epididymitis } ketoconazole 400mg PO OD x 1yr
- 6) Coccidioidomycosis
 - kidney } amphotericin B 2g IV
 - prostate } amphotericin B 2.5g IV x 4mo
 - bladder } amphotericin B 2g IV + ketoconazole 200mg PO OD x 1 yr
- 7) Histoplasmosis
 - renal } amphotericin B
 - prostate } ketoconazole 600mg/day or itraconazole 200mg/day

Antifungal Summary (Poon CD)

Pharmacology	Side Effects	Interactions & CI
Amphotericin B		
<ul style="list-style-type: none"> - Pdyn: binds to ergosterol component of fungal wall → lysis - Pkin: iv only; high protein binding <ul style="list-style-type: none"> - $T_{1/2}$ = 15 days - retained by placental tissues → prolonged drug effect - in pregnant women: 1/25 congenital anomaly (King 1998) - Resistance uncommon 	<ol style="list-style-type: none"> 1) allergic rxn <ol style="list-style-type: none"> a) anaphylaxis (lipid form) b) flu-like rxn: F/C, rigors 2) ototoxicity 3) nephrotoxicity <ol style="list-style-type: none"> a) H/A, pyuria, proteinuria b) lyte: ↓ K, Mg → arrhythmia 4) cardiac arrhythmias 5) hematologic <ol style="list-style-type: none"> a) thrombophlebitis b) anemia c) thrombocytopenia 6) congenital anomaly <ol style="list-style-type: none"> a) microcephaly 7) CNS <ol style="list-style-type: none"> a) H/A b) Seizure 	Interactions <ol style="list-style-type: none"> 1) nephrotoxins <ol style="list-style-type: none"> a) chemo b) aminoglycosides c) cyclosporine d) foscarnet e) pentamidine 2) digitalis: b/c of ↓ K
Flucytosine (5-FU)		
<ul style="list-style-type: none"> - Pdyn: converted to 5-fluorouracil → fungal protein and DNA synthesis - Pkin: GI absorption <ul style="list-style-type: none"> - $t_{1/2}$ 3-5h - renal excr. unchanged - cleared by dialysis - Resistance: 10% of <i>C. albicans</i>, 30% of other <i>Candida</i> species 	<ol style="list-style-type: none"> 1) general: N/V/D, enterocolitis 2) LFT 3) BM suppression: generalized 	Contraindications <ol style="list-style-type: none"> 1) Pregnancy
Ketoconazole		
<ul style="list-style-type: none"> - Pdyn: inhibits cytochrome P-450 metabolism → inhibits ergosterol metabolism → cell wall synthesis - Pkin: poor renal excr → low urine levels 	<ol style="list-style-type: none"> 1) General: H/A, skin rash 2) abN LFT; ↑ in children 3) ↑ triglycerides 4) steroid metabolism: <ol style="list-style-type: none"> a) adrenal insufficiency; Rx steroids (cf. CaP) b) chemical castration 	Interactions <ol style="list-style-type: none"> 1) antacids ↓ absorption (cimetidine or ranitidine) 2) ↑ [cyclosporine]
Fluconazole		
<ul style="list-style-type: none"> - Pdyn: see ketoconazole - Pkin: po or iv <ul style="list-style-type: none"> - concentrated in urine - Resistance: noted w/ prolonged use <ul style="list-style-type: none"> - ↑ resistance noted in non-<i>C. albicans</i> species 	<ol style="list-style-type: none"> 1) general: <ol style="list-style-type: none"> a) H/A, N/V 2) allergy: anaphylaxis 3) alopecia (chronic use, reversible) 4) skin <ol style="list-style-type: none"> a) rash b) Steven's Johnson 5) abN LFT (less than ketoconazole) <p>NB: no effect on mammalian steroid metabolism</p>	Interactions <ol style="list-style-type: none"> 1) ↑ [cyclosporine]

Chapter #18 – Male Reproductive Physiology

THE MALE REPRODUCTIVE AXIS

What constitutes the male reproductive axis?

- 1) hypothalamis → secretes **GnRH**
- 2) anterior pituitary → stimulated by GnRH } secretes **LH and FSH**
→ intrinsic FSH production also occurs
- 3) testis → LH stimulates Leydig cells to produce **testosterone**
→ FSH stimulates Sertoli cells to promote **spermatogenesis**

What is Inhibin B?

- 32-kD protein hormone **secreted by Sertoli cells**
- **suppresses FSH secretion** by gonadotropes in pituitary
- composed of α and β subunits
- may be the **BEST MARKER of the presence of spermatogenesis**
- may predict the presence of sperm in the testes

What is activin?

- 30-kD protein also **secreted by Sertoli cells**
- **stimulates FSH production**

Hypothalamus

What factors control the production of GnRH from the hypothalamus?

- 1) seasonal rhythm → peaks in spring
→ regulated by pineal gland
- 2) circadian rhythm → peak testosterone in early AM
→ regulated by neural connections arising from suprachiasmatic nucleus
- 3) pulsatile rhythm → peaks occur every 90-120 minutes

Pituitary

Which hormones are produced in the pituitary gland?

- 1) anterior → FSH, LH, ACTH, TSH, PRL, GH (“FLAT PiG”)
→ regulated by bloodborne factors
- 2) posterior → oxytocin and vasopressin (“POV”)
→ regulated by neural stimuli

Steroid feedback on hypothalamus and pituitary

What’s involved in the negative feedback suppression of GnRH release?

- T is metabolized by **aromatase to estradiol**
→ estradiol acts on *pituitary* to modulate FSH, LH release
- T is metabolized by **5 α -reductase to dihydrotestosterone (DHT)**
- testosterone acts on *hypothalamus* to decrease GnRH release
- **LH release is mainly mediated by testosterone**
- **FSH release is primarily mediated by estradiol**

Development of the Male Reproductive Axis

What is the embryologic origin of the testis?

- starts as a placode of the coelomic epithelium on the surface of the primitive kidney (mesonephros)
- placode grows into a gonadal ridge & primordial germ cells move into epithelium from yolk sac
- gonadal ridge develops into medullary cord
- at 7 weeks, primordial germ cells move into the medullary cord → this is 1st step separating ovarian & testicular pathways
- testis now forms seminiferous & interstitial compartments
- SRY gene product (a nuclear transcription factor) initiates male sexual differentiation
→ SRY gene is not always required for testicular development
- Sertoli cell precursors secrete Mullerian inhibiting substance (MIS) causing regression of female reproductive tract structures (Mullerian duct)
- fetal Leydig cells produce testosterone which induces differentiation of the Wolffian duct structures (epididymides, vas deferens, sex accessory glands)

Endocrinology of testis

What regulates Leydig cell function?

- **LH stimulates Leydig cells to secrete T**

What regulates Sertoli cell function and spermatogenesis?

- 1) **FSH stimulates Sertoli cells to nurture germ cells through spermatogenesis**
- 2) testosterone
- 3) paracrine signaling from peritubular cells also supports spermatogenesis

What are the main stages involved in the production of spermatozoa?

- 1) mitotic divisions that produce either a set of stem cells (resistant to external injury) or a population of rapidly proliferating germ cells (to become spermatozoa)
- 2) meiosis which results in formation of haploid gamete
- 3) differentiation of gamete into specialized and ideally suited for fertilization

What is the role of the epididymis in sperm maturation?

- ability to fertilize & capacity for motility achieved only after passing through portion of epididymis

What changes occur at puberty?

- hypothalamus **develops capacity to generate pulses of GnRH**
- nocturnal melatonin levels decrease resulting in abatement of inhibition by melatonin
- androgen -ve feedback is delayed until steroidogenic capacity of the testis is developed
- leptin levels increase to stimulate gonadotropin secretion
- GH and IGF-1 also stimulates gonadotropin secretion

Aging of the Hypothalamic and Pituitary Axis

What is the effect of aging on gonadotropins?

- **basal LH levels increase** in older men
- **pulsatility of LH is also blunted** → indicates decreased GnRH pulsatility
- higher testosterone concentrations are required in testicle to maintain steroidogenesis
- 40 yo men have lower fecundity than men less than 25 yrs of age

TESTIS

Gross Structures and Vascularization

What are the normal dimensions of the male testis?

- **15 to 25cc** and ~4.5 to 5.1cm long

What are the 3 layers surrounding the testicular parenchyma?

- 1) visceral tunica vaginalis
- 2) tunica albuginea → has some smooth muscle cells
- 3) tunica vasculosa

What is the blood supply to the testis?

- 1) testicular (internal spermatic) artery
 - penetrates tunica albuginea then travels inferiorly along the posterior surface of the testicle
 - branches pass anteriorly
 - some branches also travel over inferior pole of testis, passing anteriorly
 - counter-current exchange of heat in spermatic cord b/w artery & pampiniform plexus provides blood to testis that is 2-4°C lower than rectal temp
 - 2) deferential vasal artery
 - from **inferior vesical artery** which is a branch of internal iliac
 - 3) cremasteric artery
 - from **inferior epigastric**
- *** medial & lateral midsection of testis has fewer vessels than anterior or inferior section ***

What is the venous drainage of the testis?

- **veins DO NOT run with arteries**
- veins draining parenchyma join deferential veins and form the pampiniform plexus

What does the testicular parenchyma consist of?

- septa separates testis into compartments
- each compartment contains **seminiferous tubules (germ cells) + interstitial tissue**
 - **seminiferous tubules (sertoli cells + germ cells) accounts for ~80% of volume**
 - **interstitial tissue accounts for 20-30%** of the volume of the testicle and consists of:
 - Leydig cells (testosterone production)
 - mast cells
 - macrophages
 - nerves
 - blood vessels
 - lymphatics

What is the path taken by spermatozoa? } whole process takes 72days

- 1) seminiferous tubules → 600 to 1200 per testis
- 2) rete testis
- 3) ductuli efferentes → 6 to 12 connecting rete testis to epididymis
- 4) head/caput epididymis
- 5) body & tail of epididymis
- 6) vas deferens (convoluted then straight)
- 7) ampulla of vas

What is the innervation of the testis?

- no somatic innervation
- autonomic innervation from intermesenteric nerves & renal plexus
 - runs along testicular artery

Cytoarchitecture and Function of the Testis

What constitutes the testicular interstitium?

- 1) Leydig cells → LH stimulates T production by cholesterol transportation into mitochondria
- 2) mast cells
- 3) macrophages → involved in regulation of Leydig cells
- 4) nerves
- 5) blood vessels
- 6) lymphatic vessels
- 7) fibroblastic supporting cells

What non-pituitary factors affect Leydig cell function?

- LHRH
- inhibin
- activin
- prostaglandins
- adrenergic stimulation
- EGF, IGF, TGF

What are the 4 main reasons we have several testosterone peaks during the life cycle?

- 1) differential development of fetal reproductive tract
- 2) neonatal organization (“imprinting”) of androgen-dependent target tissues, ensuring appropriate response later in life
- 3) masculinization at puberty
- 4) maintenance of growth and function of androgen-dependent organs

What are the germinal elements seen in the seminiferous tubules?

- 1) slowly dividing primitive stem cell population
- 2) rapidly proliferating spermatogonia
- 3) spermatocytes undergoing meiosis
- 4) metamorphosing spermatids

What are the 3 layers surrounding the seminiferous tubules (peritubular cells)?

- 1) outer adventitial layer of fibrocytes
- 2) myoid cells interspersed with connective tissue lamellae → myoid cells have contractile fxn
- 3) thick inner lamella with lots of collagen

What is the structure of the Sertoli cell?

- irregular shaped nucleus
- prominent nucleolus
- sits on BM of seminiferous tubules & extends cytoplasmic ramifications towards lumen of tubule
- germ cells are arranged between the Sertoli cells

How does the Sertoli cell support germ cell development?

- 1) creates specialized microenvironment of the adluminal compartment of seminiferous epithelium
- 2) supports germ cells via gap junctions between Sertoli and germ cells
- 3) facilitates migration of differentiating germ cells
- 4) **produces androgen-binding protein (ABP)** which serves as reservoir of androgenic hormones for seminiferous tubules

What are the different levels of the blood-testis barrier?

- 1) **tight jxns between Sertoli cells**
 - **primary level of barrier**
 - also segregates pre-meiotic germ cells (spermatogonia) & young spermatocytes from other germ cells (mature spermatocytes & spermatids)
 - 2) capillary endothelial cells
 - 3) peritubular myoid cells
- *** blood-testis barrier develops at onset of spermatogenesis but germ cells NOT necessary for development of barrier *****

How does a testicular insult cause anti-sperm antibodies?

- antigens on germ cells are present only after initiation of puberty
- biopsy, torsion, trauma causes antisperm Ab production **ONLY if insult occurs after puberty**

What function does the blood-testis barrier have?

- 1) keeps stable fluid bathing germinal cells separate from fluid outside barrier
- 2) isolates haploid male gamete which is not recognized as “self” by immune system

How many spermatozoa are produced by the epithelium of the seminiferous tubules?

- 123 million spermatozoa per day

Describe the process of spermatogenesis?

- 64 days → 4 cohorts of spermatozoa each cycle (16days)
- 6 stage cycle
- 3 main phases:
 - 1) proliferative phase → **spermatogonia** divide either to
 - a) replace their numbers (stem cell renewal)
 - b) produce daughter cells committed to become spermatocytes (mitosis – q16 days)→ 2/3 of all spermatogonia undergo apoptosis
 - 2) Meiotic phase → **spermatocytes** undergo reduction division resulting in haploid spermatids (meiosis)
 - 3) Spermiogenesis → **spermatids** undergo a dramatic metamorphosis in size & shape to form **mature spermatozoa**

What are the changes that occur in the spermatid during spermiogenesis?

- 1) loss of cytoplasm
- 2) formation of acrosome
- 3) formation of flagellum
- 4) migration of cytoplasmic organelles to positions characteristic of the mature spermatozoon

How many different germ cell types exist in the testis?

→ each represents different steps in spermatogenesis

- 1) dark type A spermatogonia
 - 2) pale type A spermatogonia
 - 3) type B spermatogonia
- ↓
- ↓ MITOSIS
- ↓
- 4) preleptotene primary spermatocytes
 - 5) leptotene primary spermatocytes
 - 6) zygotene primary spermatocytes
 - 7) pachytene primary spermatocytes
- ↓
- ↓ MEIOSIS I
- ↓
- 8) secondary spermatocytes
- ↓
- ↓ MEIOSIS II
- ↓
- 9)-13) spermatids → Sa, Sb1, Sb2, Sc, Sd1, Sd2

What are the important steps in the prenatal development of the testis with respect to germ cells?

- 1) primitive germ cells called gonocytes → central location within seminiferous cords
- 2) gonocytes migrate to periphery and called spermatogonia
- 3) increased mitotic division at 8th-22nd wk of pregnancy, then again at 7-9 yrs of age

What is the role of testosterone in spermatogenesis?

- T levels in testis are ~100 fold higher than in peripheral circulation
- T initiates and qualitatively maintains spermatogenesis via effects on Sertoli cells

What are the results of hypophysectomy in men?

- Leydig cell atrophy → no LH
 - peritubular hyalinization
 - germinal depletion (no FSH + low T) ranging from only spermatogonia to scattered spermatocytes
- *** FSH is not essential for spermatogenesis but only in the presence of FSH & testosterone does quantitatively and qualitatively normal spermatogenesis occur ***

What are the specific genes that control spermatogenesis?

- Y microdeletions associated with decreased spermatogenesis
 - AZFa (DBY gene) → azoospermia with SCO pattern on Bx
 - AZFb (RBMY gene) → azoospermia with MA or hypospermatogenesis
 - AZFc (DAZ gene) → azoospermia but best chance of finding sperm on Bx

EPIDIDYMIS

Gross Structure and Contractile Tissue

Describe the structure of the epididymis

- 3-4m in total length } Wolffian duct structure
- coiled and encapsulated within sheath of convoluted tubule of the tunica vaginalis
- 3 regions:
 - head/caput → 8-12 ductuli efferentes and proximal segment of ductus epididymis
 - body/corpus → larger diameter tubule
 - tail/cauda → largest diameter tubule but with irregular shaped lumen
- epididymis is covered by contractile tissue
 - 2-4 cell thick contractile layer surrounds ductuli efferentes to proximal body of epididymis
 - distal body is surrounded by thicker contractile cells
 - tail is surrounded by thick smooth muscle cells that form 3 layers
- ductules of epididymis are lined with epithelium consisting of 2 types of cells:
 - principle cells (more numerous)
 - basal cells

Innervation

What is the innervation of the epididymis?

- primarily from **intermediate spermatic nerve (br. of superior part of hypogastric plexus)** and **inferior spermatic nerve (branch of pelvic plexus)**
- number of nerve fibers increases as you move distally towards tail

Vascularization

What is the blood supply to the epididymis?

- head & body → branch of testicular a. divides into **superior & inferior epididymal branches**
- tail → branches from **vas deferential artery**
- cremasteric artery also serves as collateral source
- arteries enter along septa formed by connective tissue of tunica vaginalis

What is the venous drainage of the epididymis?

- head → veins join pampiniform plexus or vena marginalis
- tail and body → veins join to form vena marginalis epididymis of Haberer

What is the lymphatic drainage of the epididymis?

- head and body → same as testis (to RPLN's)
- tail → join lymphatics of vas deferens to external iliac nodes

What is the blood-epididymis barrier?

- gap junctions between epithelial cells form a blood-epididymis barrier → extends head to tail

Functions of the Epididymis

What is the function of the epididymis?

- 1) sperm transport (2-12 days)
 - time through tail is same as the time it takes to get through head and body
 - transit time is independent of age
 - depends more on sperm production rate (higher = faster)
 - transport is primarily due to contractile cells surrounding epididymis NOT sperm
- 2) sperm storage
 - sperm stored in tail for varying lengths of time, depending on sexual activity
 - ~50% of epididymal sperm is in tail
 - viability lasts for several weeks in tail
- 3) maturation of spermatozoa
 - a) motility → head has mostly "immature" tail movement; in tail >50% of spermatozoa have mature motility
→ **partly time dependent but mainly due to interactions in distal regions**
 - b) fertilization → testicular spermatozoa can't fertilize unless ICSI used
→ fertility maturation occurs at level of distal body/proximal tail
→ **worst fertilizing capacity in head, best in tail**

What biochemical changes do spermatozoa undergo during transit through the epididymis?

- sperm surface membranes become more negatively charged
- oxidation of membrane sulfhydryl group to disulfide bonds
→ provides rigidity for motility and penetration
- increased capacity for glycolysis
- other post-testicular modifications of membrane components
→ ↑'d ability to adhere to zona pellucida

What is the significance of the fluid within the epididymal lumen?

- influences sperm transport, storage, and maturation
- differs from serum & changes throughout length of epididymis
→ likely due to differential vascularization along length of epididymis, semipermeable blood-epididymal barrier, & selective absorption & differential secretion along length of duct

Which hormone controls epididymal function?

- no gradient of androgen levels in different regions of epididymis
- increased levels of DHT and 5 α -reductase in epididymis
- bilateral castration results in decreased epididymal weight, changes in luminal histology, and changes in epididymal fluid
- function may also be influenced by temperature and sympathetic innervation

SPERMATOOZOA

What does the average spermatozoa look like?

- 60µm long
- oval sperm **head** (4.5µm long x 3µm wide) → consists primarily of **nucleus & acrosome**
- **connecting piece** links head to middle piece
- **middle piece** consists of highly organized helically arranged **mitochondria** surrounding set of outer dense fibers and the characteristic **9+2 microtubular structure of sperm axoneme**
- **tail (principal piece)** consists of outer dense fibers and axoneme covered by fibrous sheath
- **end piece** is only axonemes

What happens to sperm in the female genital tract?

- ejaculate is initially able to **coagulate** (seminogelin from SV) then **liquefies** due to proteases (eg PSA)
 - ? assists in passing through cervical mucous
- uterine transport takes 5-68 minutes
- **capacitation occurs within female genital tract** and results in the **acrosome reaction** and the development of hyperactivated motility
 - prostatic and SV secretions may aid in this process
 - fructose from SVs provide energy source
 - antioxidant protection from seminal fluid allows sperm to survive in hostile enviro
- spermatozoal fxn doesn't end with **fertilization** → mitotic activity of embryos is organized by paternally derived centrosome

DUCTUS VAS DEFERENS

Describe the vas deferens.

- derived from the mesonephric (Wolffian) duct
- 30-35cm in length, 2-3mm in diameter (lumen 300-500µm in diameter)
- starts at epididymal tail & terminates in ejaculatory duct near prostate
- 5 segments:
 - 1) sheathless epididymal portion
 - 2) scrotal portion (convoluted and straight)
 - 3) inguinal division
 - 4) retroperitoneal/pelvic portion
 - 5) ampulla
- 3 layers
 - 1) outer adventitial connective tissue sheet (contains blood vessels & small nerves)
 - 2) middle layer consisting of 3 layers of muscle → **vas has greatest muscle-lumen ratio (10:1) of any hollow viscus**
 - 3) inner mucosal layer

What is the blood supply to the vas deferens?

- **deferential artery → branch of inferior vesicle artery**

What is the innervation of the vas deferens?

- has both **sympathetic & parasympathetic** nerve fibers
- rich supply of sympathetic adrenergics from hypogastric nerves
- minor contribution of parasympathetic cholinergics

What type of cells are seen in the vas deferential epithelium?

→ pseudostratified epithelium

- 1) basal cells
- 2) principal cells → more common in proximal vas
- 3) pencil cells
- 4) mitochondrion-rich cells → more common in distal vas

What is the function of the vas deferens?

- more than just a passive conduit
- spermatozoal transport → sympathetics cause muscular contractions resulting in propulsion of sperm
→ **stores almost as much spermatozoa as epididymis**
- absorption and secretion
- function likely depends on androgen stimulation
 - T converted to DHT in epididymis
 - castration results in atrophy of vas
 - adrenergic stimulated contraction is altered by castration

What are the steps in fertilization?

- deposition of sperm in vagina
- penetration of cervical mucous plug
- sperm migration through uterus (5-68 minutes)
- capacitation and hyperactivation
- sperm penetration of cumulus oophorus
- sperm binding to zona pellucida
→ carbohydrate binding proteins on sperm membrane interact with species-specific ZP3 protein in egg zona pellucida
- acrosome reaction
- sperm penetration of zona pellucida
- sperm fusion with oocyte plasma cell membrane
- cortical granule exocytosis
- nuclear decondensation
- nuclear fusion
- embryo cleavage
- uterine implantation

List the components of seminal fluid. } } } “Fresh SSPPPPICEZ”

- fructose
- sperm
- spermine
- protease (eg PSA)
- proteins (eg seminogelin)
- PGs
- phosphates
- immunoglobulins
- citric acid
- esterases
- Zinc

Chapter #19 – Male Infertility

HISTORY

What is the initial w/u for male infertility?

1) History

- previous fertility/infertility hx
- sexual hx } frequency, timing, duration, birth control, use of lubricants
- developmental hx } UDT, age of puberty, gynecomastia, congenital abN'ities of GU tract
- surgical hx } vasectomy, orchidopexy, hernia sx, scrotal trauma, SCI, torsion, pelvic/scrotal sx, retroperitoneal sx, bladder neck sx
- medical hx } recent febrile illness, UTIs, STDs, viral orchitis, renal disease, DM, RADs, TB, MS, epididymitis, anosmia (pituitary), midline defects (cleft palate)
- FmHx } hypogonadism, UDT, CF, congenital midline defects
- occupational hx } laptop use, exposure to chemicals, heat, etc
- meds, allergies, smoking, EtOH, drugs
- female reproductive hx } previous pregnancies w/ other partners, menstrual hx, infertility w/u

2) Physical exam

- general } VS's, body habitus, virilization, gynecomastia (estrogen), visual fields, etc
- abdo exam } retention, masses, DRE (nodule, cystic dilation of SV)
- genital exam } penile size, meatus, testicles, epididymis, presence of vas, hernias, varicoceles
- neuro exam } motor, sensory, reflexes, peripheral neuropathy
- CV exam

3) Investigations

- semen analysis x 2
- hormonal evaluation (**if sperm [] is <10 million/cc**)
 - start with T + FSH } if abN, repeat with LH, estrogen, prolactin, TSH
 - rare to have abN endocrine findings if sperm [] is >10 million/cc
 - LH, estrogen, prolactin, TSH (especially if any indication of possible pituitary issues)
 - consider GnRH stimulation tests
- genetic testing (karyotype, CF mutation, Y microdeletions)
 - NOA & severe oligospermia } r/o Klinefelter's, AZF microdeletions
- other
 - post-ejaculatory urine (PEU) specimen
 - urinalysis & urine C&S
 - semen cultures } test for *Mycoplasma* & *Chlamydia*
 - routine C&S not indicated in absence of pyospermia or clinical symptoms
 - anti-sperm Ab
 - leukocyte staining } % of round cells → >1 million WBCs per cc is abN
- sperm functioning tests (**NOT ROUTINELY RECOMMENDED**)
 - DNA Fragmentation Index } >30% is bad
 - post-coital test (PCT) } normal is >10-20 sperm per HPF
 - acrosome reaction test } N = LOW spontaneous reaction rates (<5%)
 - + HIGH induced reaction rates (15-40%)
 - sperm penetration assay (SPA) } remove zona pellucida & assess penetration
 - hemizona assay } index <0.6 likely means sperm-zona interaction problem
 - sperm viability assay } to assess whether non-motile sperm are dead or viable
 - reactive oxygen species (ROS) testing } elevated levels can cause sperm damage

4) imaging

- TRUS (for low ejaculate volume)
- scrotal U/S (if scrotal exam is difficult or testicular mass suspected)

What is the chance of conception for a N or infertile couple?

- 1) normal → 20-25% per month
→ 75% by 6months and 90% by 1 yr
- 2) infertile couple → 25% will conceive w/o any treatment within 2 yrs
→ 1-3% per month (non-azoospermic)

What are some common infertility statistics?

- peak fertility is at 24yrs of age for both M & F
- 20% of infertility due to male factor alone
- 30-40% of infertility involve both M & F factors
- 50% of infertility cases involve female factor
→ **ovulatory dysfunction & fallopian tube abnormality account for majority**

What is the definition of infertility?

- inability to conceive after 1 yr of unprotected intercourse

What is the goal of the evaluation of an infertile man?

- 1) identify reversible conditions
- 2) identify irreversible causes that may be managed by ART using male partner's sperm
- 3) identify irreversible conditions that necessitate donor insemination or adoption
- 4) identify significant underlying medical pathology
- 5) identify genetic and/or chromosomal abnormalities that may affect either patient or offspring

What is the significance of UDT on fertility?

- unilateral → slightly decreases fertility
- bilateral → significant reduction of fertility
→ as long as orchidopexy occurs before puberty, timing isn't correlated with degree of infertility

What is the significance of testicular Ca on fertility?

- ~60% of patients with testicular Ca and testicular lymphoma have oligospermia
- spermatogenesis may take 4-5yrs to return after chemo or rads

What is the significance of a febrile systemic illness on fertility?

- can impair spermatogenesis for ~3months

What are some diseases involving the URT that are associated with male infertility?

- 1) Kartagener's syndrome
→ form of primary ciliary dyskinesia } aka "immotile cilia syndrome"
→ **immotile sperm (inner dynein arm problem)** + frequent URTIs + situs inversus
- 2) CF
→ congenital bilateral absence of vas (**CBAVD**)
→ motile sperm
- 3) Young's syndrome
→ **azoospermia (secretions block epididymis)** + frequent URTIs
→ motile sperm
- 4) Sarcoidosis
→ pulmonary disease
→ azoospermia (obstructive)

THE EVALUATION OF THE FEMALE PARTNER

Evaluation of Ovulation and the Luteal Phase

What are the methods used to evaluate ovulation?

- 1) menstrual hx → regular menstrual cycles of 21-35 days suggest regular ovulation
- 2) basal body temperature charting → drop in temp followed by a rise of at least 0.4°F for 12-15 days after ovulation is normal
- 3) progesterone levels → levels >3ng/mL suggests ovulation
- 4) urine or plasma LH levels → levels increase just prior to ovulation
- 5) endometrial Bx → can confirm ovulation
- 6) ovarian U/S → can evaluate follicular development and oocyte release
- 7) FSH → FSH level >10mIU/mL on menstrual cycle DAY3 suggests poor ovarian reserve (if age >38 or premature ovarian failure suspected)

What is the treatment for ovulation disorders?

- depends on underlying etiology
- usually involve ovulation-induction agents → eg Clomiphene citrate or gonadotropins

Evaluation of the Fallopian Tubes

What are the methods used to evaluate the Fallopian tubes?

- 1) hysterosalpingography → determines patency of tubes and normality of uterine cavity
- 2) laparoscopy → often combined with hysterosalpingography
- 3) tubal cannulation → can help confirm tubal occlusion and may be a treatment too
- 4) sonohystography → U/S combined with hysterosalpingography

What is the treatment for tubal occlusion?

- can be from PID, endometriosis, prior abdominal inflammation/surgery
- involves either surgical repair or IVF

Evaluation of the Uterus

What are the methods used to evaluate the uterus?

- rare to be the cause of female infertility
- 1) hysterosalpingography
- 2) U/S
- 3) hysteroscopy

Evaluation of the Peritoneal Cavity

What are the methods used to evaluate the peritoneal cavity?

- 1) U/S
- 2) laparoscopy → most sensitive and specific

PHYSICAL EXAM

What is important on the physical exam of the infertile male?

- body exam → gynecomastia } estrogen/androgen imbalance OR excess prolactin
- genital exam → phallus } hypospadias, severe chordee
 - testes } mass, volume/size (normal is 4x3cm or 15-25cc)
 - epididymis } presence of head, body, tail and induration or cystic dilation
 - vas deferens } presence, areas of atrophy
 - spermatic cord } varicocele
- DRE → mass, cystic dilation of SV, prostatitis

What is the grading system for varicoceles?

- Grade 1 → palpable only with Valsalva
- Grade 2 → palpable without Valsalva
- Grade 3 → visible & palpable ("bag of worms")

What is the definition of a subclinical varicocele?

- not palpable or visible AND asymptomatic
 - presence of multiple veins (≥ 1 vein is $> 3\text{mm}$) + reverse flow
- \ no study shows improved pregnancy rates after Rx of subclinical varicocele
/

What are the diagnostic methods to identify subclinical varicoceles?

- 1) venography
- 2) Duplex U/S
- 3) scrotal thermography

INITIAL BASIC LAB EVALUATION

Semen Analysis

What is the recommended method of collection of a S/A?

*** it is recommended that all patients should have at least 2-3 S/A's (AUA and ARSM '01) ***

- keep same # of days (2-5) of abstinence for each collection
 - can Δ counts, volume BUT DOES NOT Δ motility & morphology
- no creams or lubrication
- collect all specimen
- clean wide mouth containers
- can be done at home but keep warm in transit → should be given to lab ~1hr after collection

Which organs contribute to normal ejaculate?

- 1) initial fluid } glands of Littre (periurethral glands) + Cowper's glands (bulbourethral glands)
- 2) 2nd portion of ejaculate } prostate
- 3) main portion } testes, epididymis (**most of sperm**), vas, prostate, **SV (70% of overall ejaculate)**
- 4) last portion } SV

What is the significance of semen that doesn't coagulate?

- SV secretes substance responsible for coagulation (semenogelin)
- **may represent absent or hypoplastic SVs → get acidic, low volume semen w/o fructose**

What is the significance of semen non-liquefaction or hyperviscosity?

- normally liquefies in 5-20 minutes (prostatic proteases such as PSA)
- perform post-coital test } if N numbers of motile sperm in cervical mucus, disregard
 - } if only very few good quality sperm, likely will require washings + IUI

What is the DDX of low volume S/A? } } } Inadequate FOR Life

- Inadequate collection (MOST COMMON)
 - 1) short duration of abstinence, masturbation, etc
- Failure of emission/ejaculation
 - 2) sympathetic denervation, RP, SCI, DM, MS, etc
 - 3) psychiatric problem
- Obstruction
 - 4) absence of vas or SVs
 - 5) obstructed ejaculatory ducts
- Retrograde ejaculation
 - 6) BN surgery
 - 7) meds (α -blockers)
- Low production
 - 8) androgen deficiency/hypogonadism

What is the DDX of azoospermia?

1) NON-OBSTRUCTIVE

- a) pre-testicular (2%) } hypogonadotropic hypogonadism (“ICE Pick Pituitary”)
 - Idiopathic
 - Congenital } Kallman’s syndrome, Laurence-Moon-Bardet-Biedl, Prader-Willi, etc
 - Estrogen excess } obesity, adrenal tumour, Sertoli cell or Leydig cell tumour, etc
 - Prolactin excess
 - Pituitary disease } tumour, surgery, radiation, trauma, infection, etc
 - b) testicular (50-90%) } spermatogenic abnormalities
 - idiopathic
 - congenital } Down’s syndrome
 - “DUNKY } UDT
XX” } Noonan’s syndrome
 - } Klinefelter’s syndrome (XXY)
 - } Y microdeletions
 - } XX maleness, XYY supermale
 - acquired } Torsion
 - “TV OGR” } Varicocele
 - } Orchitis (viral)
 - } Gonadotoxins (eg macrobid, sulfasalazine, CCBs, cocaine, Chemo, etc)
 - } Radiation
- c) post-testicular (rare)
 - ejaculatory dysfunction
 - retrograde ejaculation

2) OBSTRUCTIVE (~40%)

- CBAVD
- bilateral obstruction (eg vasectomy)
- ED cyst
- epididymal obstruction

What is the DDX of oligospermia? } rarely found as an isolated abnormality

- 1) androgen deficiency
- 2) idiopathic (most common)
- 3) varicoceles (most common when oligo found w/ other abnormal semen parameters)
- 4) partial obstruction
- 5) testis Ca
- 6) gonadotoxins

What is the DDX of asthenospermia (<50% N motility)? } “VAG-PPISSS”

- 1) Varicoceles (most common)
- 2) Anti-sperm Ab’s
- 3) GU infections
- 4) Prolonged abstinence
- 5) Partial ductal obstruction
- 6) Idiopathic
- 7) Spermatozoal ultrastructural defects (eg Kartagener’s)
- 8) Systemic illness
- 9) Spermicides } lubricants, toxic contaminants in container

What is the DDx of teratospermia?

- **rarely found in isolation** } usually found with oligospermia & asthenospermia
- 1) drugs, heat, toxins (temporary insults to spermatogenesis)
 - 2) varicoceles
 - 3) absence of acrosome (rare)
 - 4) partial obstruction
 - 5) UDT

What is the DDx of oligoasthenoteratospermia (OAT)? } } “VIP USED OAT”

- **most common S/A in infertile w/u**
- 1) Varicoceles (most common)
 - 3) Idiopathic
 - 7) Partial ejaculatory duct obstruction (associated low semen volume)
 - 2) UDT
 - 5) Systemic infection
 - 6) Endocrine abnormality
 - 4) Drugs, heat, toxins

What is the significance of frequent sperm agglutination?

- suggests presence of anti-sperm Abs

What is the significance of the acrosomal index?

- the percentage of sperm with normal acrosomes
- significantly lower IVF fertilization rates if < 5-15% → >50% fertilization if >5-15%

What are the S/A findings that suggest ejaculatory duct pathology?

- low volume
- acidic pH → acidic prostatic secretions (SV secretions are alkaline)
- low fructose (<120mg/dL)

What are the S/A findings that suggest obstruction?

- low volume azoospermia
- acidic pH
- no fructose
- semen doesn't coagulate (from lack of SV fluid)

What is the DDX of low fructose levels (<120mg/dL) in semen?

- 1) inflammation of SVs
- 2) androgen deficiency
- 3) partial obstruction of ejaculatory ducts
- 4) incomplete ejaculation

What is the WHO criteria for normal semen parameters?

- 1) **volume** → >2.0 mL
 - 2) **concentration** → ≥20 million/mL (avg is 70-100 million/mL)
 - 3) **counts** → ≥40 million per ejaculate
 - 4) **morphology** → ≥30% normal shape (≥14% according to Kruger strict criteria)
 - 5) **motility** → ≥50% normal at 1hr (50% A + B or 25% A only)
 - 6) **pH** → ≥7.2
 - 7) **WBC's** → ≤1 million per mL (round cells)
 - 8) **viability** → ≥75%
 - 9) **fructose** → >13 μmol per sample
- should also assess semen coagulability, liquefaction, viscosity
- motility type A = progressive straight forward motility
- motility type B = progressive non-linear forward motility

What are the criteria for normal sperm morphology by RIGID criteria?



Head

Length: 5–6 μm

Width: 2.5–3.5 μm

Acrosome: 40%–70% of head

Midpiece

Width $\leq 1 \mu\text{m}$

Length 1.5 x head length

Tail

Approximately 45 μm long

Uniform

Thinner than midpiece

Uncoiled

Free from kinks

Cytoplasmic droplets

Less than one half of head area

In midpiece only

Hormonal Evaluation

What hormones are part of the usual hormone evaluation?

- FSH and LH
- Testosterone (AM)
 - can add bioavailable T
- prolactin
- TSH
- estrogen

When is a hormone evaluation indicated?

- **when sperm [] is <10 million/mL**

What is the significance of FSH in the evaluation of infertility?

- if elevated, indicates spermatogenesis problem } no –ve feedback from inhibin (made by Sertoli cells)
- if normal, doesn't guarantee normal spermatogenesis

What is the DDX of MILDLY elevated prolactin (<50ng/mL)?

*** prolactin levels in patients with prolactinomas are very high → >50ng/mL ***

- renal failure
 - stress
 - meds
 - thyroid dysfunction
 - chest wall irritation
- } no treatment recommended as it doesn't improve fertility

List clinical features of hyperprolactinemia

- oligomenorrhea/amenorrhea
- infertility
- galactorrhea
- sexual dysfunction } decreased libido, ED
- visual problems
- H/A
- decreased TSH

What are the findings of excessive estrogen?

- bilateral gynecomastia
- ED
- atrophic testes
- low T → estradiol stimulates liver to produce SHBG, which lowers level of bioavailable T
 - estradiol also increases prolactin levels

DIAGNOSTIC ALGORITHMS BASED ON THE INITIAL EVALUATION

Absent or Low-volume Ejaculate

What is the difference between aspermia & azoospermia?

- aspermia → complete absence of seminal fluid
- azoospermia → absence of sperm within the seminal fluid

What is the DDX of aspermia?

- **SCI (most common cause)**
- retroperitoneal surgery (sympathetic damage)
- DM
- MS
- psych disturbances

What is the DDX of low volume S/A? } } } Inadequate FOR Life

- Inadequate collection (MOST COMMON)
 - 1) short duration of abstinence, masturbation, etc
- Failure of emission/ejaculation
 - 2) sympathetic denervation, RP, SCI, DM, MS, etc
 - 3) Psychiatric problem
- Obstruction
 - 4) CBAVD or absence of SVs
 - 5) obstructed ejaculatory ducts
- Retrograde ejaculation
 - 6) BN surgery
 - 7) meds (α -blockers)
- Low production
 - 8) androgen deficiency/hypogonadism

What is the w/u for low ejaculate volume?

- 1) **repeat semen analysis** (minimum 2 days abstinence +/- Sudafed)
 - r/o incomplete collection
 - check for fructose (acidic + unilateral absence of vas + no fructose = absence of SVs)
 - 2) **post-ejaculatory urinalysis (pellet)**
 - r/o retrograde ejaculation
 - a) +ve (10-15/HPF) → sympathomimetics (eg Sudafed) or bladder wash + IUI
 - b) -ve for sperm → **TRUS**
 - i) normal → vibrostim/EEJ (failure of emission/ejaculation)
 - ii) obstruction → **SV aspiration** (also do CF testing)
 - (SV >1.5cm) +ve → TURED (indigo carmine)
 - ve → TURED + VE or IVF/ICSI
- for bladder washing, need to alkalinize urine to increase survival of sperm
 - **SVs >1.5cm means obstruction**
 - **SV aspiration with >3 motile sperm/hpf is diagnostic of ED obstruction**
 - can perform TURED in 2 ways }
 - 1) under TRUS guidance
 - 2) inject indigo carmine into SVs, remove TRUS and resect until blue dye seen in urethra

Azoospermia

What is the DDX of azoospermia?

- 1) NON-OBSTRUCTIVE
 - a) pre-testicular (2%) } hypogonadotropic hypogonadism ("ICE Pick Pituitary")
 - Idiopathic
 - Congenital } Kallman's syndrome, Laurence-Moon-Bardet-Biedl, Prader-Willi, etc
 - Estrogen excess } obesity, adrenal tumour, Sertoli cell or Leydig cell tumour, etc
 - Prolactin excess } hyperT4, stress, estrogens, pituitary tumour
 - Pituitary disease } tumour, surgery, radiation, trauma, infection, etc
 - b) testicular (50-90%) } spermatogenic abnormalities
 - idiopathic
 - congenital ("DUNKY XX") } Down's syndrome
 - } UDT
 - } Noonan's syndrome
 - } Klinefelter's syndrome (XXY)
 - } Y microdeletions
 - } XX maleness, XYY supermale
 - acquired ("TV OGR") } Torsion
 - } Varicocele
 - } Orchitis
 - } Gonadotoxins (eg macrobid, sulfasalazine, CCBs, cocaine, Chemo, etc)
 - } RADs
 - c) post-testicular (rare)
 - ejaculatory dysfunction
 - retrograde ejaculation
- 2) OBSTRUCTIVE (10-50%)
 - CBAVD
 - ED cyst
 - bilateral obstruction (eg vasectomy)
 - Epididymal obstruction

Table 19-3 -- Hormonal Status as a Function of Clinical Diagnosis

Clinical Status	FSH (mIU/mL)	LH (mIU/mL)	Testosterone (ng/dL)
Normal men or obstruction	Normal	Normal	Normal
Isolated spermatogenic failure	↑	Normal	Normal
Testicular failure	↑	↑	Normal or ↓
Hypogonadotropic	↓	↓	↓
hypogonadism			

What is the w/u for azoospermia?

- 1) **repeat S/A**
 - exam pellet to r/o severe oligospermia
- 2) **P/E** to assess presence of vas & size of testicles
 - if CBAVD → CFTR testing + IVF/adoption (+ abdo U/S if CF -ve to r/o renal agenesis) (95% of M with CF have CBAVD)
 - if unilateral AVD → abdo U/S to r/o renal agenesis +/- CF testing
 - if vas present but testes small → think non-obstructive azoospermia
 - if vas present and testes large/N → think obstructive azoospermia
- 3) **serum T + FSH**
 - a) elevated FSH (2x UL of N) → 1° testicular failure
 - microTESE/IVF
 - genetic testing (Klinefelter's, Y microdeletions)
 - b) low FSH & T → hypogonadotropic hypogonadism
 - serum LH + prolactin + CT/MRI head
 - c) normal → **testicular Bx to r/o obstructive azoospermia**
 - i) normal → obstructive azoospermia
 - VV or VE
 - ii) abN → microTESE/IVF, donor insemination, adoption

What is the w/u for Low volume Azoospermia?

- 1) **repeat S/A**
 - r/o incomplete collection
 - exam pellet to r/o severe oligospermia
 - check for fructose (acidic + unilateral absence of vas + no fructose = absence of SVs)
→ CF testing if absent SVs
- 2) **P/E** to assess presence of vas & size of testicles
 - if CBAVD → CFTR testing/genetic counselling + IVF/adoption (abdo U/S if CF -ve to r/o renal agenesis)
 - if CUAVD → abdo U/S to r/o renal agenesis + CF testing
 - if vas present but testes small, think non-obstructive azoospermia
 - if vas present and testes large/N, think obstructive azoospermia
- 3) **serum T + FSH**
 - a) elevated FSH → 1° testicular failure
 - microTESE/IVF
 - genetic testing (Klinefelter's, Y microdeletions)
 - b) low FSH & T → hypogonadotropic hypogonadism
 - serum LH + prolactin + CT/MRI head
 - c) normal → **post-ejaculatory urinalysis (pellet)**
 - r/o retrograde ejaculation
 - a) +ve (10-15/HPF) → sympathomimetics (eg Sudafed) or bladder wash + IUI
 - b) -ve for sperm → **TRUS**
 - i) N → **testicular Bx to r/o obstructive azoospermia**
 - a) N → vasography
 - obstructed → VV or VE
 - unobstructed → vibrostim/EEJ (failure of emission/ejaculation)
 - b) abN → microTESE/IVF, donor insemination, or adoption
 - ii) obstruction → **SV aspiration** (also do CF testing)
 - +ve → TURED (indigo carmine)
 - ve → TURED + VE or IVF/ICSI

Oligospermia

What is the DDx of oligospermia? } rarely found as an isolated abnormality

- 1) **idiopathic (most common)**
- 2) **varicoceles (most common when oligo found w/ other abnormal semen parameters)**
- 3) partial obstruction
- 4) testis Ca
- 5) gonadotoxins
- 6) androgen deficiency

What is the w/u of isolated oligospermia?

- 1) **repeat S/A**
- 2) **P/E to r/o varicocele**
 - varicocelectomy if present
- 3) **serum FSH, testosterone (if concentration is <10 million/mL)**
 - a) both abnormal → full hormonal evaluation
 - b) only elevated FSH → abnormal spermatogenesis (1° testicular failure)
→ TESE/IVF, donor insemination, adoption

Asthenospermia

What is the DDx of asthenospermia (abN motility <50%)? } } "VAG-PPISSS"

- 1) **Varicoceles (most common)**
- 2) **Anti-sperm Ab's**
- 3) **GU infections**
- 4) **Prolonged abstinence**
- 5) **Partial ductal obstruction**
- 6) **Idiopathic**
- 7) **Spermatozoal ultrastructural defects (eg Kartagener's)**
- 8) **Systemic illness**
- 9) **Spermicides } lubricants, toxic contaminants in container**

What is the w/u for isolated asthenospermia?

- 1) **repeat S/A**
→ r/o prolonged abstinence & toxic contaminants in collection container
- 2) **Anti-sperm Ab assay**
 - a) -ve → **motility testing**
 - if >5% normal → r/o varicocele, heat, systemic illness, infection
 - semen cultures for *Mycoplasma genitalium* or urine DNA testing for *C. trachomatis*
 - urinalysis + urine C&S
 - if <5% normal → **sperm viability assay**
 - i) high → EM to r/o ultrastructural defect (eg Kartagener's)
 - ii) low → **TRUS**
 - N → r/o varicocele, heat, systemic illness, infection
 - abN → **SV aspiration**
+ve → TURED
 - b) +ve → immunosuppression
 - low overall efficacy with ++ risk of side effects
 - IVF/ICSI

What are some genetic disorders associated with ASTHENOSpermia?

- 1) Kartagener's syndrome (primary ciliary dyskinesia) } chronic RTIs, infertility, situs inversus (50%)
- 2) retinitis pigmentosa } incurable disease causing blindness due to abnormalities in photoreceptors
- 3) Usher's syndrome } retinitis pigmentosa + progressive deafness

Teratospermia

What is the DDx of teratospermia?

- **rarely found in isolation** } usually found with oligospermia & asthenospermia
- 1) drugs, heat, toxins (temporary insults to spermatogenesis)
 - 2) varicoceles
 - 3) absence of acrosome (rare)
 - 4) partial obstruction
 - 5) UDT

Normal Semen Parameters

What is the DDx of infertility with normal semen parameters?

- 1) female factors
- 2) immunologic infertility (anti-sperm Ab's)
- 3) incorrect coital habits
- 4) unknown

What is the w/u of infertility with normal semen parameters?

- 1) **repeat S/A**
 - 2) **refer female to ob/gyne**
 - 3) **post-coital test** → N sperm } unexplained infertility (if female also normal)
 - a) anti-sperm Ab's in female and male
 - b) sperm function testing (ie sperm penetration assay or acrosome reaction test)
 - if normal → IVF/ICSI
- shaking sperm } anti-sperm Ab's
- no sperm } improper coital technique

CLASSIFICATION OF MALE INFERTILITY STATUS BY CRITERIA OF SEMEN ANALYSIS

- | | |
|--|---|
| <p>I. Low Ejaculate Volume</p> <ul style="list-style-type: none">A. MedicationsB. Retroperitoneal or bladder neck surgeryC. Ejaculatory duct obstructionD. Diabetes mellitusE. Spinal cord injuryF. Psychologic disturbancesG. IdiopathicH. Incomplete collection <p>II. Azoospermia</p> <ul style="list-style-type: none">A. Hypogonadotropic hypogonadism<ol style="list-style-type: none">1. Kallmann's syndrome2. Pituitary tumorB. Spermatogenic abnormalities<ol style="list-style-type: none">1. Chromosomal abnormalities2. Y chromosome microdeletions3. Gonadotoxins4. Varicocele5. Viral orchitis6. Torsion7. IdiopathicC. Ductal obstruction<ol style="list-style-type: none">1. Congenital bilateral absence of the vas deferens2. Vasal obstruction3. Epididymal obstruction4. Ejaculatory duct obstruction | <p>III. Oligoasthenoteratospermia (OAT)</p> <ul style="list-style-type: none">A. VaricoceleB. CryptorchidismC. IdiopathicD. Drugs, heat, toxinsE. Systemic infectionF. Endocrinopathy <p>IV. Normal but Infertile</p> <ul style="list-style-type: none">A. Gynecologic abnormalityB. Abnormal coital habitsC. Acrosomal defectsD. Antisperm antibodiesE. Unexplained <p>V. Asthenospermia</p> <ul style="list-style-type: none">A. Spermatozoal structural defectsB. Prolonged abstinenceC. IdiopathicD. Genital tract infectionE. Antisperm antibodiesF. VaricoceleG. Partial obstruction |
|--|---|

Table 19-5 -- Distribution of Patients Presenting with Infertility by Findings on Semen Analysis

<i>Semen Pattern</i>	<i>No. Patients</i>	<i>%</i>
Normal	297	14
Azoospermia	299	14
Multiple parameters abnormal	1040	49
Single abnormal parameter		
Asthenospermia	127	6
Teratospermia	85	4
Oligospermia	83	4
Low volume	149	7
Pyospermia	42	2

→ **MOST COMMON S/A IN THE INFERTILE MALE IS MULTIPLE PARAMETER ABNORMALITY (ie OAT)**

Table 19-6 -- Distribution of Patients by Diagnostic Category after Full Evaluation

<i>Category</i>	<i>No. Patients</i>	<i>%</i>
Varicocele	806	38
Idiopathic	482	23
Obstruction	271	13
Normal	197	9
Cryptorchidism	73	3
Testicular failure	54	3
Antisperm antibodies	42	2
Ejaculatory dysfunction	49	2
Gonadotoxin[*]	43	2
Endocrinopathy	25	1
Pyospermia	22	1
Genetic/chromosomal[†]	11	0.5
Torsion	11	0.5
Erectile dysfunction	8	0.4
Testis cancer	9	0.4
Ultrastructural	7	0.3
Viral orchitis	7	0.3
Systemic illness	4	0.2
Hypospadias	1	0.05

→ **VARICOCELE IS THE MOST COMMON FINDING IN MALE INFERTILITY EVALUATION**

ADDITIONAL TESTING

Anti-sperm Ab's

What prevents the formation of anti-sperm Ab's?

- at puberty, **tight jxns** develop between the Sertoli cells in the seminiferous tubules
→ also from **endothelial cells** in capillaries + **peritubular myoid cells**

What are the RFs for developing anti-sperm Ab's? }}} "Very Careful, BUT GOT Ab's"

- 1) Varicoceles
- 2) Cancer of testis
- 3) **Bx** or surgery of testis
- 4) UDT
- 5) Torsion
- 6) GU tract infection (mumps, epididymitis)
- 7) Obstruction of the ductal system
 - vasectomy → 60% develop anti-sperm Ab's
 - CBAVD → 1/3 have anti-sperm Ab's
- 8) Trauma to GU organs
- 9) Anal intercourse (receptive)

What are the indications for anti-sperm Ab testing?

- 1) risk factors
- 2) asthenospermia (shaking)
- 3) sperm agglutination
- 4) abnormal post-coital testing
- 5) couples with unexplained infertility

What are the different methods of detecting anti-sperm Ab's?

- mixed agglutination reaction (MAR) assay (direct or indirect)
- immunobead assay (direct or indirect)
- 1) direct assays → **detect presence of Ab's on the patient's sperm**
 - have the benefit of only detecting sperm-bound immunoglobulins
 - **the preferred test**
- 2) indirect assays → measure Ab's in the patient's serum
 - presence of serum Ab's don't always mean Ab's are present on sperm
 - needs anti-sperm Ab negative donor sperm
 - advantage is that it yields amount of Ab bound to sperm

How do anti-sperm Ab's affect sperm function?

- motility
- cervical mucous penetration
- capacitation
- acrosome reaction
- binding to and penetration of the zona pellucida
- oolemma binding

How common are anti-sperm Ab's?

- found in 10% of infertile males
- found in 2% of fertile males

Leukocyte Staining

What are round cells?

- **EITHER immature germ cells (spermatocytes) or leukocytes**
→ can't be differentiated without special stains
- **>1million WBCs/mL is abN**
- 30% of patients with increased # of round cells have true pyospermia ... rest have increased # of immature germ cells

What is the significance of leukocytes in semen?

- associated with GU infection or inflammation
- higher in infertile couples
- doesn't correlate with fertility rates or the presence of pyospermia
- many patients with pyospermia don't have GU infections

What are the different methods of leukocyte staining?

- Papanicolaou stain
- monoclonal Ab's directed against WBC surface antigens
- detecting presence of peroxidase withing WBCs

What are the indications for leukocyte staining?

- if >10-15 round cells/HPF
- >1 million round cells/mL
- *** **investigate for GU tract infection if >1million WBC/mL *****

What is the management of pyospermia in the absence of GU tract infection?

- anti-inflammatories
- empirical Abx } tetracycline or doxycycline
- frequent ejaculations
- prostatic massage
- semen processing + IUI or IVF

Semen Cultures

What is the significance of GU tract infections and infertility?

- uncommon cause of male infertility } **can lead to asthenospermia**
- asymptomatic GU tract infection may or may not be related to infertility

What are the indications for genital tract cultures?

- clinical symptoms suggestive of GU tract infection
- documented pyospermia on S/A
- isolated asthenospermia on S/A

Which bacterium are considered to have deleterious effects on semen parameters?

- *Mycoplasma genitalium*
- *Chlamydia trachomatis*

Chromatin/DNA Integrity Testing

What is the role of sperm chromatin (DNA)?

- fertilization is followed by sperm nucleus decondensation
- paternal gene expression (DNA transcription) occurs mainly at 4 cell embryonic stage
- defects in chromatin organization may lead to infertility

What are the RFs for abnormal sperm DNA? }}} “Infertility FACTS”

- male Infertility
- Fever
- Air pollution
- Cancer
- Toxic industrial exposure
- Smoking

How does sperm DNA damage occur?

- 1) defective repair mechanism of single-stranded DNA nicks
- 2) abnormal protamine function or content
- 3) abnormal apoptosis of cells with double-stranded DNA breaks
- 4) oxidative stress

How is the extent of DNA damage measured?

- 1) TUNEL assays → labels sites of DNA breaks with dUTP attached to a marker
→ DNA fragmentation can be determined
→ depending on marker, can use:
 - 1) flow cytometry
 - 2) fluorescent microscopy
 - 3) light microscopy
- 2) comet assay → fluorescent DNA-binding dye used to identify DNA breaks
→ the more DNA breaks, the longer the fluorescent tail
- 3) sperm chromatin structure assay (SCSA) → damaged DNA lights up green and is measured by flow cytometry
→ doesn't directly measure DNA breaks
→ measures DFI (red/red+green)

What is the significance of DNA Fragmentation Index (DFI)?

- correlates with pregnancy rates
 - DFI 0%-15% → accounted for 75% of pregnancies that occurred in 1 yr
 - DFI 15%-30% → accounted for 22% of pregnancies that occurred in 1yr
 - **DFI >30% → accounted for only 3% of pregnancies that occurred in 1yr**
- *** Evenson et al, 1999 ***

Ultrastructural Evaluation

What ultrastructural defects are seen on light microscopy?

- gross tail abnormalities
- acrosomal defect
- complete absence of acrosome

What ultrastructural abnormalities can only be seen by electron microscopy?

- | | | |
|---------------------------------|---|--|
| - defects in mitochondria | \ | - result in absent or very low motility |
| - defects in outer dense fibers | } | - most are viable |
| - abnormal microtubules | / | - need sperm viability assay to determine if dead or alive but nonmotile |

What are the indications to perform EM on S/A?

- motility <5-10% associated with reasonably high viability

Radiologic Evaluation

What is the role of imaging in the infertile male?

- to identify complete or partial ductal obstruction
- complete obstruction → usually azoospermic
- partial obstruction → can have oligospermia, asthenospermia, and/or early demise of sperm after ejaculation
→ very hard to differentiate partial ductal obstruction from other causes of male infertility (especially idiopathic oligospermia)

What is the role of vasography?

- used to identify site of obstruction in;
 - 1) azoospermic men that have Bx proven spermatogenesis
 - 2) severely oligospermic men with suspicion of unilateral vasal obstruction
eg hernia repair with abnormal contralateral testis
- **should only be performed in conjunction with reconstructive surgery**
 - proximal patency of epididymis → presence of sperm in intravascular fluid
 - distal patency → NS +/- dye
 - dilute contrast } N if contrast seen throughout vas, SV, ejaculatory duct & bladder
 - passage of 2-0 monofilament

What is the role of TRUS?

- used when suspicious of ejaculatory duct obstruction
- can visualize prostate, SVs, and ampullary portion of vas deferens
- obstruction suggested when SVs are dilated
 - abN if >1.5cm in diameter
 - don't always see dilated SVs) need vasography or SV aspiration
 - **>3 motile sperm/hpf is diagnostic of ED obstruction**
- **S/A in obstruction is:**
 - 1) **low volume (<1mL)**
 - 2) **absent fructose**
 - 3) **acidic pH (<7.2)**
 - 4) **failure to coagulate (no SV secretions)**

What is the role of venography?

- used to detect and potentially treat varicoceles
- right femoral or right internal jugular access
 - R internal jugular preferred if embolization planned
- +++ false-positives & false-negatives
 - can get false +ve if you cannulate vein or use high pressure
 - can get false -ve if not done in reverse Trendelenburg or if there's reflux from collateral veins not seen
- mainly reserved to document and embolize recurrence after varicocele repair OR during primary embolization of varicocele

What is the role of scrotal U/S?

- used mainly to diagnose varicoceles when P/E is equivocal or it's difficult to examine pt
- also used to r/o testicular tumours in high-risk patients
- no role for scrotal U/S to identify subclinical varicoceles
- colour Duplex → clinical if >3-5mm and reversal of blood flow with Valsalva

What is the role of abdominal U/S?

- used to assess kidneys
- ipsilateral renal anomalies found in 80% of men with **unilateral absence of vas**
 - renal agenesis is most common (~25% of those with CUAVD)
- not needed for patients with CBAVD + CFTR gene mutation (**95% of M with CF have CBAVD**)
 - can have renal anomalies if CBAVD that is NOT related to CF

Sperm Function Testing

What are the normal parameters of a post-coital sperm-cervical mucous interaction test?

- 1) **>10-20 sperm/HPF**
- 2) **majority of sperm should have progressive motility**

What is the DDx of an abnormal PCT?

- inappropriate timing → just before ovulation when cervical mucous thin and clear
- anatomic abnormalities → hypospadias
- semen or cervical mucous anti-sperm Ab's
- inappropriate coital technique
- abnormal semen

What are the indications for performing a PCT?

→ no consensus on how test should be performed, timing, or grading

- 1) hyperviscous semen
- 2) unexplained infertility
- 3) low volume semen with normal total sperm counts

What is the management for couples with an abnormal PCT?

- IUI

What is the role of acrosome reaction testing?

- normal semen → spontaneous acrosome reaction rates <5%
→ induced acrosome reaction rates of 15-40%
- infertile men → HIGH spontaneous acrosome reaction rates
→ LOW induced acrosome reaction rates

What are the indications for acrosome reaction testing?

- 1) unexplained poor fertilization rates with IVF
- 2) unexplained infertility

What is the management for couples with acrosome reaction defects?

- IVF + ICSI

What is the role of Sperm Penetration Assays (SPA)?

- remove zona pellucida and count # of penetrations per hamster ova
→ interaction with zona pellucida is species-specific
- tests normal sperm }
 - 1) capacitation
 - 2) acrosome reaction
 - 3) fusion with oolemma
 - 4) incorporation into ooplasm
- **doesn't test abN sperm-zona interactions**

What are the indications for SPA?

- 1) to r/o fertilization defect when only abN'ity is morphology
- 2) unexplained infertility

What is the management of couples with an abnormal SPA?

- IVF + ICSI (no IUI or conventional IVF)

What other sperm function tests are used to assess the infertile male?

- 1) hemizona assay → split zona pellucida in half and place one half with patient sperm & other half with sperm from fertile donor
 - compare rates of bound sperm
 - **hemizona index <0.6 likely means sperm-zona interaction problem**
 - test not often used because of IVF+ICSI
- 2) Sperm viability assay → used to determine if sperm are dead or viable but nonmotile
 - used when sperm motility <5-10% (ultrastructural defects possible)
 - **can be used to select viable sperm to be injected during IVF+ICSI when sperm are nonmotile**
 - live sperm don't pick up dye (intact cell membrane) & swell in hypo-osmotic solution (maintain osmotic gradient)
- 3) Reactive Oxygen Species Testing → elevated levels of ROS can cause sperm damage
 - measure ROS vs antioxidant capacity

Genetic Testing

What are the genetic causes for male infertility?

- 1) karyotypic abnormalities → structural or numerical chromosomal abnormalities
 - 6% of infertile men have chromosomal abnormalities
 - 10-15% in azoospermic men
 - 4-5% in oligospermic men
 - sex chromosomal abnormalities mostly in azoospermic men
 - eg Klinefelter's XXY
 - autosomal abnormalities mostly in oligospermic men
- 2) Y chromosome microdeletions → found in the long arm of Y chromosome
 - 7% of infertile men have Y microdeletions
 - 13% in azoospermic men
 - 3-7% in oligospermic men
 - deletions in AZFa (SCO) and AZFb (maturation arrest) carry worse prognosis of sperm retrieval compared to AZFc deletions (hypospermatogenesis)
- 3) gene mutations → CFTR gene mutation
 - Kartagener's
 - androgen insensitivity
 - Kallman's syndrome

What are the indications for genetic testing?

- 1) severe oligospermia (<5million/mL) + candidate for ART
- 2) non-obstructive azoospermia + candidate for ART

Testicular Bx

What are the indications for testicular Bx?

- 1) diagnostic } ie azoospermia + N hormone profile + N-sized testes + ≥1 palpable vas
 - r/o obstruction
 - usually combined with VV or VE
- 2) diagnostic AND therapeutic } ie azoospermia + elevated FSH + bilaterally small testes
 - usually NOA
 - usually combined with sperm retrieval

*** if congenital absence of vas with normal FSH and normal-sized testes then you SHOULD NOT do Bx because invariably normal spermatogenesis ***

What is the role of diagnostic testicular Bx?

- **only in azoospermic men to r/o obstructive azoospermia** } N FSH, N size, ≥ 1 N vas
- usually done bilaterally but if testicular asymmetry then done on larger testis
- not recommended if suspicious of testicular failure } ie high FSH + small bilateral testes
- occasionally done to r/o partial ductal obstruction in patients w/ severe oligospermia, N testes, N FSH
- in most cases, the Bx DOES NOT give etiology of infertility

What is the role of therapeutic testicular Bx?

- **management of patients with non-obstructive azoospermia who are considering sperm retrieval for IVF**
- can give prognostic info and can cryopreserve sperm for later use in IVF

What does normal testicular parenchyma display?

- seminiferous tubules separated by thin layer of Leydig cells, blood vessels, lymphatics, and connective tissue
- Sertoli cells and spermatogonia line the BM of the seminiferous tubules

What are the normal steps of spermatogenesis?

- 1) mitotic division of stem cells → spermatogonia become spermatocytes
- 2) meiotic division of germ cells → primary become secondary spermatocytes, which become spermatids
- 3) spermiogenesis or the development of a spermatozoon → spermatids become spermatozoa

What are the different patterns seen on testicular Bx?

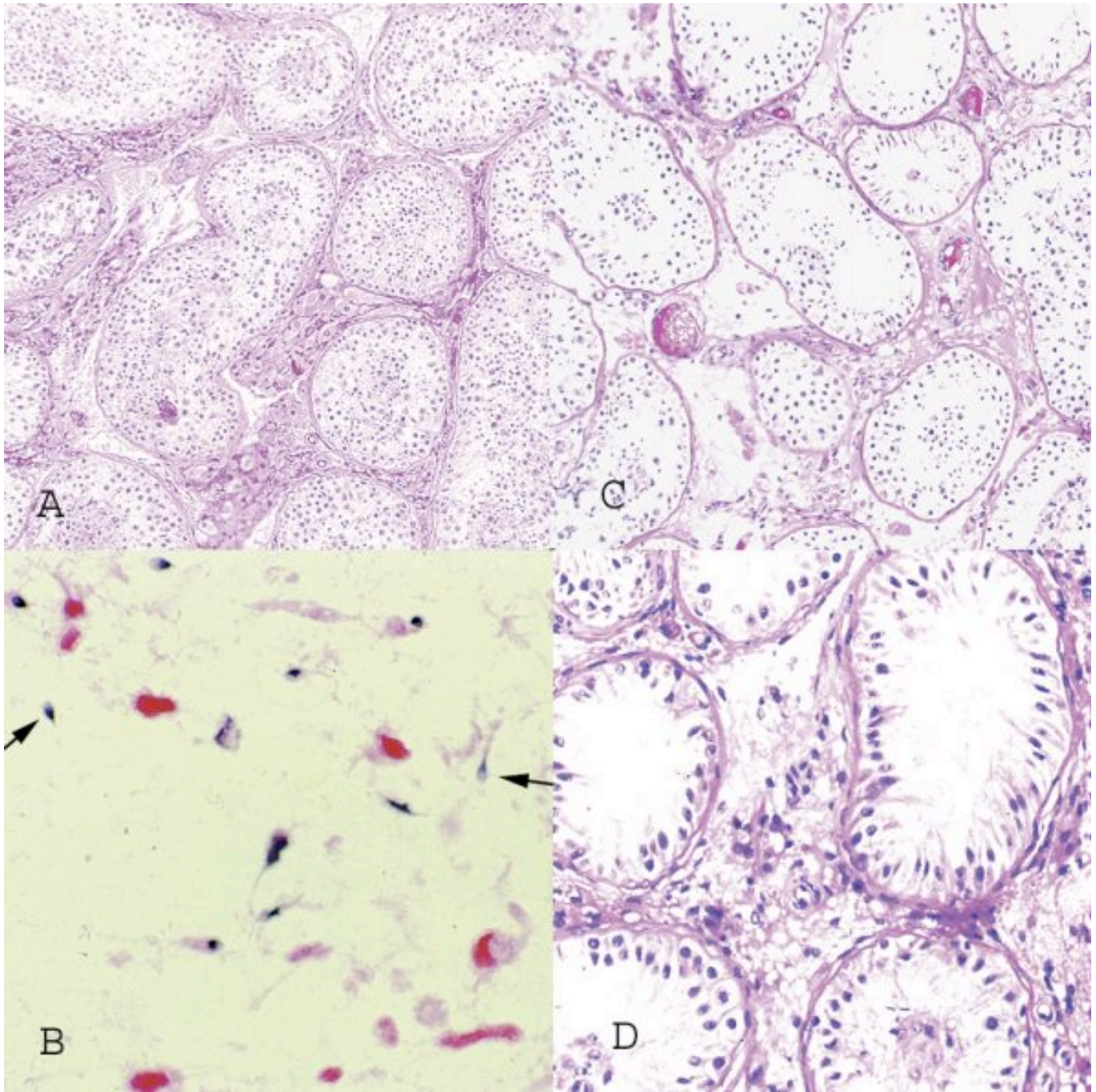
- can see a mixture of patterns within one specimen
- 1) normal testes → found in obstructive azoospermia
 - can get dilated, thick-walled seminiferous tubules with long term obstruction
- 2) hypospermatogenesis → often get oligospermia but can have azoospermia rarely
 - reduction in # of all germinal elements within tubules
 - normal Leydig cells
- 3) maturation arrest → azoospermic
 - consistent arrest at one stage of spermatogenesis
 - ie primary spermatocyte, secondary spermatocyte, spermatid
 - difficult to distinguish N spermatogenesis from late maturation arrest
 - normal Leydig cells
- 4) Sertoli cell-only syndrome → azoospermic patients w/ small to N testes & N to elevated FSH
 - seminiferous tubules with only Sertoli cells and NO germ cells
 - Leydig cells usually minimally altered
 - “wind-swept” appearance
- 5) End-stage testes → azoospermia with bilateral atrophic and firm testes
 - tubular and peritubular sclerosis with NO germ cells
 - Sertoli cells may or may not be present
 - Leydig cells may be absent or decreased in #

What other patterns are seen on testicular Bx?

- hypogonadotropic hypogonadism → small tubules w/ **no germ cells except immature spermatogonia & Leydig cells**
- isolated LH deficiency (fertile eunuchs) → normal or **hypospermatogenesis**
 - **reduced Leydig cell numbers**
- hypophysectomized adult males → **testicular atrophy**
 - normal-sized tubules with depletion of germ cells
 - depleted or absent Leydig cell

Which fixatives are acceptable for testicular Bx?

- 1) Bouin's
 - 2) Glutaraldehyde
 - 3) Zenker's
- \ } **formalin is NO GOOD**
/



→ A = NORMAL
B = NORMAL MATURE SPERMATOOZA

C = COMPLETE EARLY MATURATION ARREST
D = SCO PATTERN ("wind-swept")

How can one classify causes of male infertility?

1) Endocrine causes (Pre-testicular)

- ## 2) Disorders of spermatogenesis (Testicular)

- Genetic } prune belly, myotonic dystrophy, AIS

- Congenital } UDT, intersex, bilateral anorchia, SCO syndrome

- Vanishing testis syndrome

- Testicular torsion

- Varicocele

- Orchitis

- Gonadotoxins } Chemo/radiation, Heat, Environmental toxins, Medications, Idiopathic

3) Disorders of sperm delivery (Post-testicular)

- #### 4) Sperm function disorders

- immunologic disorders (eg Antisperm Ab's)

- ultrastructural abnormalities of sperm

Endocrine Causes

What are the endocrine causes of infertility?

- aka pretesticular causes
- secondary to either hormone deficiency, hormone excess, or receptor abnormalities

What is the significance of pituitary disease and infertility?

- pituitary function can be affected by:
 - surgery
 - infarction
 - tumours
 - radiation
 - infectious disease
- prepubertal disease results in growth retardation, delayed puberty, adrenal and thyroid deficiency
- pituitary tumours can present with infertility, ED, visual field disturbances, and severe H/As
- **small & soft testes** (vs small and firm in primary testicular failure)
- **T usually low or low normal and FSH, LH are low**

What is the significance of isolated hypogonadotropic hypogonadism and infertility?

- 1) **idiopathic hypogonadotropic hypogonadism**
 - no known cause
 - 2) **Kallmann syndrome (congenital hypogonadotropic hypogonadism + anosmia)**
 - hypothalamus can't produce GnRH } X-linked recessive
 - infertility
 - delayed puberty (hallmark)
 - N or slightly tall
 - gynecomastia
 - micropenis (50%)
 - UDT
 - small testes
 - renal anomalies
 - craniofacial anomalies (cleft palate, congenital deafness, etc)
- Rx → androgens for sexual development
→ gonadotropins (hCG, FSH) for spermatogenesis
→ GnRH therapy only effective in patients with intact native pituitary gland

What is the significance of the Fertile Eunuch Syndrome and infertility?

- isolated LH deficiency (normal FSH, low testosterone)
- no Leydig cells due to lack of LH } no testosterone
- lack of virilization, large testes, small-volume ejaculates, oligospermia

What is the significance of isolated FSH deficiency and infertility?

- N virilization
 - N LH and testosterone levels
 - N testes
 - oligospermia, azoospermia } usually have <5million/mL
- Rx → recombinant human FSH for spermatogenesis

What other congenital syndromes are associated with infertility?

- **Prader-Willi syndrome (15q11-13)**
 - obesity
 - hypotonic musculature
 - mental retardation
 - small hands and feet
 - short stature
 - hypogonadism
- **Laurence-Moon-Bardet-Biedl syndrome**
 - hypogonadotropic hypogonadism
 - retinitis pigmentosa
 - polydactyly
 - hypomnesia
 - anosmia
 - short
- **CHARGE syndrome**

What is the significance of estrogen excess & infertility?

→ peripheral estrogens suppress pituitary gonadotropin secretion causing **2° testicular failure**
eg estrogen-secreting adrenal or testis tumours, hepatic dysfunction, obesity

- ED
- gynecomastia
- testicular atrophy

Rx → aromatase inhibitors (eg ketoconazole)

What is the significance of androgen excess & infertility?

→ androgen excess causes hypogonadal state by -ve feedback, leading to **2° testicular failure**

1) exogenous androgens

eg anabolic steroids

3) endogenous androgen production

eg CAH → most common cause of endogenous androgen excess

→ 21-hydroxylase deficiency is most common cause of the 5 enzyme defects

→ lack of cortisol results in increased ACTH production

→ get elevated serum 17-hydroxyprogesterone levels & urinary 17-ketosteroids

→ increased ACTH leads to an excess of adrenal androgens

→ short stature

→ precocious puberty

→ small testes

→ testicular adrenal rest tumours

Rx → glucocorticoids

eg testicular or adrenal tumours

What is the significance of PROLACTIN EXCESS and infertility?

- results in ED and male infertility

- **caused by:**

→ **pituitary tumour**

→ **meds (dopamines, INH, TCA)**

→ **idiopathic**

→ **stress**

→ **elevated TSH**

→ **medical illness (renal failure, cirrhosis)**

- low FSH, LH

- low testosterone

Rx → bromocriptine, cabergoline (recommended)

→ surgery, rads

What is the significance of thyroid disease and infertility?

- hyperT4 alters spermatogenesis and sex steroid hormone metabolism

- hypoT4 effects are more subtle and reversible

What is the significance of GLUCOCORTICOID EXCESS and infertility?

- cortisol excess may suppress LH, leading to androgen deficiency and testicular dysfunction

- **hypospermatogenesis and maturation arrest**

What is the significance of androgen abnormalities and infertility?

- may involve;

1) deficiency in androgen synthesis } get ambiguous genitalia

2) deficiency in conversion of T to DHT (5 α -reductase deficiency) } get ambiguous genitalia

3) androgen receptor abnormalities } eg AIS

What is AIS?

→ X-linked genetic disorder caused by mutation in androgen receptor gene

→ 46, XY male w/ phenotypes ranging from pseudohermaphroditism to N male with infertility

→ elevated testosterone levels

Disorders of Spermatogenesis

What diseases can effect spermatogenesis?

- chromosomal disorders
- UDT
- testicular torsion
- varicocele
- orchitis
- chemo or rads
- bilateral anorchia (vanishing testis syndrome)
- myotonic dystrophy
- Sertoli Cell-only syndrome
- drugs, meds, gonadotoxins
- heat, environmental toxins, occupational exposure

What chromosomal disorders affect spermatogenesis?

- 1) Klinefelter's Syndrome → **47, XXY (can have mosaicism 46, XY/47, XXY)**
 - 1 in every 600 male births
 - phenotypic M w/ **small, firm testes (testicular atrophy in most)**
 - get ↓'d Leydig cell number but seems like Leydig cell hyperplasia due to atrophy of seminiferous tubules
 - tall stature + gynecomastia
 - **elevated FSH, LH, estradiol**
 - **N testosterone in 50%, otherwise low**
 - delayed completion of puberty
 - **azoospermia**
 - higher risk of **breast cancer, DM, CVD**
 - Rx → microTESE + IVF/ICSI (sperm found 50% of time)
- 2) Noonan's syndrome → **46, XY**
 - look similar to Turner's
 - short stature + webbed neck + low set ears + hypertelorism
 - cardiovascular anomalies
 - **UDT + testicular atrophy**
 - **elevated FSH, LH with low T**
 - Rx → adoption/donor sperm
- 3) Y chromosome microdeletions → microdeletions on long arm of Y chromosome
 - associated with **azoospermia or severe oligospermia**
 - AZFa (proximal) → least common microdeletion (USP9Y, DBY, etc)
 - poor prognosis for sperm retrieval (SCO)
 - AZFb (middle) → RBMY gene deletion
 - poor prognosis for sperm retrieval (MA)
 - AZFc (distal) → most common microdeletion
 - DAZ gene deletion
 - best prognosis for sperm retrieval (hypospermat.)
 - there's now an AZFd
 - microdeletions passed onto male offspring
 - Rx → IVF/ICSI
- 4) XX male → **46, XX**
 - small firm testes + small to N-sized penis with increased incidence of hypospadias
 - gynecomastia + shorter than N height
 - **azoospermia**
 - **elevated FSH, LH and low testosterone**
 - Rx → adoption/donor sperm
- 5) XYY syndrome → **47, XYY**
 - **tall men w/ increased incidence of UDT & hyospadias** } ?aggressive, criminal behaviour
 - **severe oligospermia or azoospermia**
 - **maturation arrest or Sertoli cell-only on Bx**
 - **normal FSH, LH , and testosterone**
 - Rx → ART

Who should be offered karyotype analysis?

- unexplained infertility
- male partners of women with recurrent miscarriages

What is the effect of bilateral anorchia (aka vanishing testis syndrome) on spermatogenesis?

- found in genetic XY males with nonpalpable testes
 - have prepubertal male phenotypes (androgens and MIS were present in utero)
 - testes lost in utero due to infection, torsion, or vascular injury
 - elevated FSH, LH and low testosterone
- Rx → testosterone for virilization + adoption/donor sperm

What is the effect of UDT on spermatogenesis?

- present in 3-4% of full term newborns and ~1% in 1yr olds } unlikely to descend after 6 months
 - 2/3 of cases unilateral, 1/3 bilateral → 50% of bilateral and 25% of unilateral cryptorchid patients have sperm []'s <12-20 million/mL
 - get **decreased # of Leydig cells and germ cells**
 - higher the undescended testicle, the more testicular dysfunction
 - no germ cells in 90% of intra-abdo testes vs 20-40% of inguinal
 - retractile and ectopic testes are NOT associated with testicular dysfunction
- Rx → surgical correction before 1-2 yrs of age
- higher fertility with corrected unilateral cryptorchidism (debatable)

How does testicular torsion affect spermatogenesis?

- 1 in 4000 men under the age of 25
- severity of semen abnormalities related to duration of torsion
- there may be abnormalities even in contralateral normal testes

What affect do varicoceles have on spermatogenesis?

- **most common correctable cause of male infertility → most with varicoceles ARE fertile**
- found in 15% of early adults → 20-40% in men presenting with infertility
- 90% left sided, 10% bilateral
- varicoceles due to venous occlusion (eg RCC + IVC thrombus) DO NOT collapse when in supine position
- varicoceles associated with **impaired testicular growth**
- associated with **decreased motility in 90%** of men and **decreased sperm []'s in 65%**
- see increased **abN morphology also (tapered forms)**

Rx → varicocelectomy

- get improved semen parameters (70%) and ↑'d testicular volume
- conception rates average ~40-50% (vs baseline 30%)
- ~10% of azospermic patients get enough sperm after Sx for IUI

Why are varicoceles more common on the left?

- 1) left gonadal vein enters left renal at right angle
- 2) absence of venous valves more common on left side
- 3) left renal vein more susceptible to compression between SMA and aorta
 - "nutcracker phenomenon"

List theories on how varicoceles impair fertility

- 1) ↑'d intratesticular temperature
- 2) reflux of renal & adrenal metabolites
- 3) ↓'d blood flow & hypoxia
- 4) paracrine hormonal insufficiency
- 5) impaired growth

List effects of a varicocele on the testis.

- 1) testicular growth failure
- 2) Leydig cell dysfunction
- 3) semen abN'ities } OAT, azoospermia, isolated asthenospermia
- 4) histologic changes } tubular thickening, interstitial fibrosis, MA, etc

What are the indications for varicocelectomy?

- 1) adolescents with grade 2 or 3 varicoceles + ipsilateral testicular growth retardation
 - 2) clinically detectable varicocele + abnormal S/A in infertile couple (normal female)
 - 3) clinically detectable varicocele + abnormal S/A in M who may want to conceive in future
 - 4) symptomatic varicocele
 - 5) ?cosmetic reasons
- *** known infertility, female normal or with correctable cause of infertility, abnormal semen parameters, clinically palpable varicocele, or suspicious exam + positive imaging ***

What is the effect of Sertoli Cell-only syndrome (SCOS) on spermatogenesis?

- seminiferous tubules with no germ cells
- small to normal testes
- **azoospermia**
- **elevated FSH with normal testosterone and LH**
- pure (congenital) and mixed (acquired) SCOS → mixed better prognosis
- **can successfully retrieve sperm in 50% of SCOS patients**

What are the causes of SCOS?

- **idiopathic (most common)**
- Y microdeletions
- karyotypic abnormalities
- UDT
- orchitis
- chemo or Rads
- estrogen Rx

Table 19-8 -- Proposed Differences between Pure SCOS and Acquired SCOS

	<i>Pure (Congenital) SCOS</i>	<i>Mixed (Acquired) SCOS</i>
Cytokeratin	Absent	Present
Telomerase	Absent	May be present
Sertoli cells' morphology	Normal	Abnormal
Basement membranes	Thin (normal)	Thickened or edematous
Hyalinization of tubules	Absent	Often present
Seminiferous tubule size	Normal	Small and variable
Cytoplasmic lipid granules in Sertoli cells	Rare	Common
Immature germ cells found in semen	Never	Possible
Spermatogenesis present in some sections of the testes	Never	Sometimes

What affect does orchitis have on spermatogenesis?

- mumps associated with 30% of orchitis patients, if contracted before puberty
 - permanent testicular atrophy may develop within several months to several yrs after infection
 - may also be due to syphilis, gonorrhea, leprosy, and mononucleosis
- Rx → IFN treatment during orchitis decreases likelihood of atrophy
- long-acting GnRH analog
 - TESE + IVF/ICSI

What is the effect of CHEMO on spermatogenesis?

- affects most actively dividing cells → spermatogonia and spermatocytes
- combination of drugs used, duration of Rx, age of patient are major determinants of effect
- **alkylating agents have worst effect** on spermatogenesis (eg cisplatin, cyclophosphamide)
- **develop azoospermia and elevated FSH**
- pre-Rx spermatogenic impairment seen in patients with leukemia, lymphoma, and testis CA
- 25% of testis cancer patients have pre-Rx dysfunction in contralateral normal testis
- after cisplatin-based chemo, **most recover spermatogenesis within 4 yrs**
- **no increased risk of birth defects**
- bank sperm before, not during, chemo → chromosomal aneuploidy seen during chemo

What is the effect of RADs on spermatogenesis?

- germ cells are very radiosensitive → spermatids more resistant than spermatogonia & spermatocytes
- **Leydig cells are relatively radio-resistant → testosterone levels normal**
- **semen quality returns to normal within 2 yrs after RADs for seminoma**
- **25% become permanently infertile**
- **no increased risk of birth defects**

What affect does myotonic dystrophy have on spermatogenesis?

- get delayed muscle relaxation after contraction
- **80% develop testicular atrophy → Leydig cells not affected so only see elevated FSH**
- sterile even before atrophy when men have apparent normal semen parameters
- also associated with cataracts, cardiac conduction defects, baldness, and mental retardation

What affect does heat have on spermatogenesis?

- heat is detrimental to spermatogenesis
- recommend avoiding saunas, Jacuzzis, or hot tubs → type of underwear NOT issue

What environmental toxins and occupational exposures effect spermatogenesis?

- lead
- cadmium
- mercury
- pesticides
- arsenic
- hydrocarbons
- amebicide soil fumigants

Which drugs, medications, and gonadotoxins are detrimental to spermatogenesis?

- “Cocaine & Marijuana SSNAACCKSS”
- Cocaine → decreased sperm counts
- Marijuana → decreased testosterone, gynecomastia, decreased sperm []’s, pyospermia
- Smoking → decreased semen parameters (pregnancy rates affected more by female smoking)
- Sulfasalazine → decreased sperm [] and motility (use 5-ASA for IBD instead)
- Nitrofurantoin (chronic high doses) → maturation arrest
- Anti-androgens
- Alcohol → testicular atrophy, decreased # of germ cells, decreased bioavailable T, ED
- Colchicines → oligospermia
- Cimetidine → degeneration of germ cells (use ranitidine instead)
- CCBs → affects sperms ability to fertilize egg (no effect on production)
- Ketoconazole
- Steroids → testicular atrophy
- Spironolactone → causes ED and infertility (anti-androgen activity)
- chronic opioid use → hypogonadotropic hypogonadism (low testosterone and FSH)
- finasteride ???
- caffeine → NOT DETRIMENTAL ... controversy → may affect motility

What is the significance of idiopathic male infertility?

- **25% of patients with abN semen parameters have no identifiable etiology**
- empirical medical therapy shown to be ineffective → if started, continue for 3-6 months
- 26% with abnormal semen parameters get pregnant WITHOUT any treatment

What empirical medical therapies have been tried for idiopathic male infertility?

- none have been shown to be consistently effective
- FSH or LH therapy
- GnRH therapy → only good for Kallmann syndrome
- clomiphene citrate and tamoxifen (anti-estrogens)
- androgens
- vitamins/anti-oxidants
- anti-inflammatories

Sperm Delivery Disorders

What is the significance of ductal obstruction and infertility?

- found in 7-12% of infertile men → more common in azoospermic patients
- can be bilateral or unilateral and may occur at multiple locations
- unilateral obstruction is risk factor for developing anti-sperm Ab's

What are the causes of ductal obstruction?

- 1) congenital → malformation or absence of ductal structures
 - eg CBAVD → **most common cause of obstructive azoospermia**
 - SVs are often absent or hypoplastic
 - can see renal anomalies (more common w/ unilateral vasal agenesis)
 - **low volume, acidic, azoospermia**
 - Rx → sperm retrieval (MESA) + IVF/ICSI
 - CF testing and counseling
 - (95% of M with CF have CBAVD)**
 - eg B/L complete ED obstruction → **low volume, fructose –ve, acidic, azoospermia**
 - hard to Dx partial ED obstruction
 - TRUS + SV aspiration
 - Rx → TUR ejaculatory duct
- 2) acquired → infection, iatrogenic injury, or vasectomy

What are the predictors of successful VV/VE? (includes AUA Update #6 – 2008)

- 1) patient factors
 - obstruction <3yrs
 - med/surg hx post-vasectomy
 - prior fertility
 - presence of sperm granuloma
 - long testicular remnant length
 - good quality sperm in vasal fluid
 - watery fluid at vasectomy site
- 2) partner factors
 - prior fertility
 - age <35yrs

What is the DDx of ED obstruction?

- 1) congenital } atresia, stenosis, utricular/mullerian/wolffian duct cyst
- 2) acquired } trauma, infection, inflammation, iatrogenic (eg TURP)

What diseases can cause ejaculatory problems?

- suspect ejaculatory problem in patients with **low volume or absent ejaculate**
- r/o anorgasmia
- post-ejaculate urine for sperm → **+ve if 10-15 sperm/HPF**
- 1) failure of emission → SCI, MS, retroperitoneal sx
 - Rx → penile vibratory stimulation (70% ejaculate) → good for lesions above T10
 - rectal probe ejaculation (75% ejaculate) → 2nd line, watch for autonomic dysreflexia
- 2) retrograde ejaculation → BN surgery, TURP, DM, MS
 - Rx → meds if no hx of Sx or failure of emission eg ephedrine, imipramine, etc
 - urinary sperm retrieval + IUI if refractory retrograde ejaculation or if surgical changes to BN

Sperm Function Disorders

What is the management strategy for immunologic infertility?

- 1) suppress Ab formation → corticosteroids (don't improve fertility in most)
 - 2) use of spermatozoa without Abs for ART → chymotrypsin to digest off Ab's
- Rx → IUI + chymotrypsin
→ IVF/ICSI

What is the significance of ultrastructural abnormalities of sperm?

- 1) **defects seen on electron microscopy** → defects in outer dense fibers, microtubules, mitochondria, connecting piece, acrosome
 - 2) **defects in flagellum** → immotile but viable sperm
→ **most common defect involves complete absence of both inner and outer dynein arms of axoneme**
→ can be associated with defects of cilia of respiratory tract
 - primary ciliary dyskinesia
 - if associated with situs inversus also then called Kartagener's
 - 3) **defects in sperm head** → round-headed sperm (globozoospermia) can't fertilize egg
 - 4) **defects of connecting piece** → separation of head from tail
- Rx → IVF/ICSI

ASSISTED REPRODUCTIVE TECHNIQUES

Technique	Abbreviation
Intrauterine insemination	IUI
In vitro fertilization	IVF
Intracytoplasmic sperm injection	ICSI
Microsurgical epididymal sperm aspiration	MESA
Percutaneous sperm aspiration	PESA
Testicular sperm extraction	TESE
Testicular sperm aspiration	TESA

*** involves manipulation of sperm, ova, or both

*** usually also involves superovulation (controlled ovarian hyperstimulation, COH)

Is IVF + ICSI the most cost effective treatment strategy?

- varicocelelectomy more cost effective
- post-vasectomy, reversal is more cost effective → even repeat reversal after failure is more cost effective
- IUI more cost effective

Semen Processing

What are some of the methods of sperm processing prior to ART?

- simple sperm washing
- swim-ups
- sedimentation
- centrifugation

Intrauterine Insemination (IUI)

What is IUI?

- injection of processed sperm into uterus
- don't use raw semen → seminal PGs may cause severe uterine cramping & may get pelvic infection
- can use natural cycle insemination or superovulation (if abnormal semen parameters)
- **need AT LEAST ~2 million motile sperm after processing**

What are the indications for IUI?

- 1) male factor infertility
- 2) unexplained infertility
- 3) cervical mucous abnormalities
- 4) anatomic abnormalities interfering with deposition of sperm at cervical os
eg severe hypospadias, retrograde ejaculation
- 5) anatomic abnormalities interfering with intercourse

What are the complications of IUI?

- uterine cramping → usually self limited
- pelvic infections → <0.5%
- allergic reaction to insemination media → rare
- multiple gestations if superovulation used → 15-30%

IVF

What is IVF?

- superovulation used to recruit multiple oocytes
- ova harvested after ovulation via U/S-guided needle aspiration
- insemination performed in-vitro by mixing processed sperm (~100,000 sperm) with retrieved oocytes
- developing embryos incubated for 2-3 days then placed transcervically into uterus
→ recommended to transfer 2-4 embryos
- if incubated for 5 days and transferred at blastocyte stage, higher implantation rates (but fewer embryos make it to day 5)
- **only 20-30% of transferred embryos will lead to pregnancy**
- IVF + ICSI → allows for fertilization with very low numbers of sperm
→ 20-37% clinical pregnancy rates } ~10% if female >40yrs of age
- miscarriage rate is ~15% in women <35yrs and 30% in women >40yrs
- multiple gestations in ~40% of pregnancies

What are the indications for IVF + ICSI?

- 1) severe male factor infertility
- 2) prior failed or poor fertilization during regular IVF cycles
- 3) significant fertilizing ability defects (eg sperm-zona interaction issues)

What are the side effects of IVF + ICSI?

- low birth weight singletons
- MSK defects
- CV defects
- hypospadias
- multiple gestations in ≥30%

Sperm Retrieval

What are the different methods of retrieving sperm?

- MESA (micro epididymal) → for obstructive azoospermia
- PESA (perc) → for obstructive azoospermia
 - less invasive than MESA but less sperm retrieved
- microTESE → for non-obstructive azoospermia
 - higher chance of finding sperm, and more sperm can be found than with percutaneous methods

Do pregnancy rates differ between OA and NOA?

- yes } lower pregnancy rates for NOA

Is there a difference between fresh & frozen epididymal sperm for IVF/ICSI?

- no difference in men with obstructive azoospermia
- ??? difference in men with NOA
 - main advantage of frozen over fresh is **lower rate of HIV transmission**
 - might have slightly lower per cycle pregnancy rates with frozen sperm

Chapter #20 – Infertility Surgery

DIAGNOSTIC PROCEDURES

Indications for Testicular Biopsy

What are the indications for testicular Bx?

- 1) diagnostic } ie azoospermia + normal hormone profile + normal-sized testes
 - r/o obstruction
 - usually combined with VV or VE
 - 2) diagnostic AND therapeutic } ie azoospermia + elevated FSH + bilaterally small testes
 - usually NOA
 - usually combined with sperm retrieval
- *** if congenital absence of vas with normal FSH and normal-sized testes then you SHOULD NOT do Bx because invariably normal spermatogenesis ***

What is the role of testis Bx in NOA?

- single Bx not indicative of entire testis or contralateral testis
- inadequate tissue for Dx in 8%
- Bx usually part of sperm retrieval

Open Testicular Biopsy (Diagnostic): Surgical Technique

Describe an open testicular Bx?

- either under local, spinal, or GA
- cord block → don't injure testicular artery or cause cord hematoma
 - concentrate on freezing vas
- freeze skin and tunica vaginalis over testis
- 1-2cm incision down to parietal tunica vaginalis → scissors used to enter tunical sac
- inject local into tunica albuginea (0.5cc)
- place 5-0 PDS/prolene at one end of proposed incision site
- 5mm incision into tunica albuginea
- excise extruded seminiferous tubules with "no touch" technique and place in buffer solution
 - Bouin's, Zenker's, or collidine buffered glutaraldehyde } NO formalin
- +/- touch imprint (more predictive) or wet prep
- close tunica albuginea with the 5-0 PDS/prolene on end of incision
- close tunica vaginalis with absorbable (5-0 PDS)
- reapproximate dartos muscle with 2-0 chromic
- subcuticular 4-0 vicryl

Percutaneous Testicular Bx

Describe a percutaneous testis Bx

- local into skin and tunica vaginalis
- puncture skin with scalpel to prevent inclusion of skin in specimen
- use prostate Biopsy gun and **aim from anterior LP toward UP, slightly lateral**
 - **medial or lateral UP may be best site to do open Bx**

What are the disadvantages of percutaneous testis Bx?

- increased risk of injury to testicular artery or epididymis
- fewer seminiferous tubules for examination
- NOT good for pts with previous scrotal surgery with scarring

Testicular Sperm Aspiration

What are the advantages of FNA of testis?

- least invasive technique for sperm retrieval
- least painful
- 21-23 gauge needle used to aspirate at least 3 different sites

What are the disadvantages of FNA of testis?

- provides only cytologic, NOT histologic, info about testis

Complications

What are the potential complications of testicular Bx?

- 1) bleeding and formation of hematoma (most common)
- 2) inadvertent Bx of epididymis → **causes obstruction**
- 3) damage to testicular artery w/ testicular atrophy → 5%
- 4) inadequate tissue sampling
- 5) chronic orchalgia

PROCEDURES TO IMPROVE SPERM PRODUCTION

Varicocele Repair

How common are varicoceles?

- 15% of normal male population
- 40% of infertile men → 70% of patients with 2° infertility
- 12% of men with normal S/A but 25% of men with abnormal semen parameters (WHO '92)
- associated with impairment of testicular function and fertility
- associated with progressive impairment

What are the grades of varicoceles?

- Grade 1 → palpable only with Valsalva
- Grade 2 → palpable without Valsalva
- Grade 3 → visible through scrotal skin at rest

What is the classification of varicoceles?

- 1) clinical → palpable on P/E
→ suspected on P/E and confirmed on U/S
- 2) subclinical → only detectable on imaging

What are the imaging modalities used to Dx varicoceles?

*** **P/E is still gold standard** ***

- 1) colour-Doppler U/S → >2.7mm or >3.0mm with reversal of flow after Valsalva
- 2) spermatic venography
- 3) radionuclide scanning
- 4) thermography

What are the indications for varicocelectomy?

- 1) adolescents with grade 2 or 3 varicoceles + ipsilateral testicular growth retardation
- 2) clinically detectable varicocele + abnormal S/A in infertile couple (normal female)
- 3) clinically detectable varicocele + abnormal S/A in M who may want to conceive in future
- 4) symptomatic varicocele
- 5) ?cosmetic reasons
- *** known infertility, female normal or with correctable cause of infertility, abnormal semen parameters, clinically palpable varicocele, or suspicious exam + positive imaging ***

What are the different approaches to varicocelectomy?

- 1) scrotal approach → historical approach
→ high risk of injury to artery & high rate of failure (complex pampiniform plexus)
- 2) retroperitoneal approach → ligation of internal spermatic vein as it exits inguinal canal with preservation of internal spermatic artery
→ transverse abdo incision at level of internal ring, 2 fingerbreadths medial to ASIS
→ enter retroperitoneum & reflect peritoneum medially to expose internal spermatic vessels
→ **recurrence is common (15%)**
- 3) lap approach → same as retroperitoneal approach
→ rarely used in adults due to invasiveness & because often involves ligation of artery
→ incise peritoneum lateral to spermatic cord and dissect out & ligate testicular vein
→ some advocate ligation of all spermatic vessels b/c testis has other arterial supply
→ recurrence rate <2%
→ hydrocele in 5%
- 4) inguinal approach → 1-4cm oblique incision made just above ext inguinal ring
→ open ext oblique aponeurosis } watch out for ilioinguinal nerve
→ mobilize cord and pass Penrose beneath
→ open internal and external spermatic fasciae around cord
→ ligate dilated veins (2-0 silk or clips) but preserve lymphatics + arteries
→ ligate any external cremasteric veins also
- 5) subinguinal approach → 2-3cm transverse incision made over ext inguinal ring
→ identify cord as it exits external ring
→ mobilize cord and pass Penrose beneath
→ open internal and external spermatic fasciae around cord
→ ligate dilated veins including cremasterics
→ less morbidity but more difficult due to increased # of branches
- 6) percutaneous embolization

What are the advantages of the microsurgical varicocelectomy?

- ↓'d rate of post-op hydrocele → rare vs ~20%
- ↓'d recurrence rate → 1-2% vs 9-15%

What are the advantages & disadvantages of the inguinal & subinguinal varicocelectomy?

- | → inguinal | → subinguinal |
|--------------------------------|----------------------------------|
| - less veins/branches | - more veins/branches |
| - longer (need to open fascia) | - faster (no need to open canal) |
| - easier to see artery | - more arterial branches |
| - more painful | - less painful |
| - hard if prior inguinal Sx | - more complex procedure |

What is the role of percutaneous embolization of varicoceles?

- performed with either coils, balloons, or sclerotherapy } femoral or internal jugular vein
- slightly higher recurrence rate → ~10%
- particularly useful in recurrent or persistent varicocele (when anatomy needs to be clarified)

What are the results of varicocelectomy?

- most studies show improved S/A & fertility } only 2 RCTs → Madgar '95 (benefit), Nieschlag '98 (trend)
- the larger the varicocele, the more likely the improvement in semen quality
- **first improved counts, then motility**; less commonly morphology improvement
- can also improve testosterone levels and decrease FSH
- if also grade 1 on contralateral side, fixing both is better than fixing unilateral grade 2-3 only

What are the pre-op predictors associated with pregnancy post-varicocelectomy?

- 1) **no testicular atrophy**
- 2) motility >60%
- 3) **sperm count >50 million per ejaculate**
- 4) FSH <300ng/mL (CAN)

What are the potential complications of varicocelectomy?

- 1) hydrocele → from lymphatic obstruction
→ least common with microsurgical approach and embolization
→ **most common with non-microsurgical inguinal**
- 2) recurrence → **highest with retroperitoneal**, non-microsurgical inguinal, and embolization
→ **lowest with micro inguinal**
- 3) testicular atrophy → uncommon esp after microsurgical (<1%)
- 4) ilioinguinal nerve injury
- 5) vas deferens injury
- 6) infection
- 7) bleeding/hematoma
- 8) hernia

What is the f/u after varicocelectomy?

- S/A at 4/12 post-op
- observe semen for 1yr post-op } if persistent or recurrent Vx then can re-operate or embolize

PROCEDURES TO IMPROVE SPERM DELIVERY

Vasectomy & Vasectomy Reversals

How common are vasectomies?

- 12% of men 20-40yrs of age have had a vasectomy
- ~5% of men will want reversal

What are the different approaches to performing a vasectomy?

- 1) conventional incision → bilateral transverse incisions or midline raphe incision
→ leave incisions open to prevent hematoma
 - 2) no-scalpel vasectomy → pull vas to midline and grasp with vas clamp
→ sharp curved mosquito used to split skin, then spread to expose vas
→ once vas free, clamp with mosquito and mobilize
→ place clips and divide
→ replace vas ends, coagulate edges of dartos layer and leave split skin as is
 - 3) percutaneous vasectomy → chemical occlusion with cyanoacrylate and phenol
→ place Congo red in R vas, methylene blue in L vas
- urine post-op should be brown
- if urine red, right missed; if urine blue, left missed
 - 4) High-frequency U/S vasectomy
 - 5) Laparoscopic vasectomy → combined with intra-abdo procedure (eg hernia repair)
 - 6) open-ended vasectomy → high failure rate but ↓'s epididymal obstruction b/c no pressure
- *** contraception until 2 negative S/A's at 3 months, 4 weeks apart ***

What is the w/u for a vasectomy?

- Hx } occupation (how much activity), how sure about not having kids, relationship status, hx of orchidopexy (Fowlers-Stevens), bleeding disorders
- P/E } general physical + focused genital exam
 - testicular size, consistency
 - presence of vas, varicoceles, testis tumours, hernia
- counseling } considered an irreversible form of contraception, risks, post-op care (no straining, S/A's, use of contraception, scrotal supports, etc)
- investigations } NONE if healthy

Describe the main points of a vasectomy?

- isolate vas from spermatic cord vessels and bring to skin
- local anesthetic injected into skin and within peri-vasal sheath
- vas delivered into incision
- deferential artery, veins, and accompanying nerves are dissected free of vas and spared
- segment of vas removed
- ends are clipped or tied +/- cauterized +/- intraluminal cautery
 - **fascial interposition has been proven to decrease recanalization rates**
- hemostasis + close

What are the potential complications following vasectomy?

→ **less common with no-scalpel technique (AUA Update #22 – 2008)**

→ early

- hematoma (most common – 2%)
- infection
- injury to testis, epididymis
- sperm granuloma } higher risk of recanalization (likely develops in all men eventually)
 - } presence associated with less epididymal & testicular damage
 - } predicts higher likelihood of VV success

→ long-term

- **chronic testicular or epididymal pain } 1 in 1000**
- altered testicular function
- testicular atrophy (cord injury)
- chronic epididymal obstruction
- anti-sperm Ab's } detectable levels found in 60-80%
- failed vasectomy (recanalization - <1%) } any motile sperm at 3 months
- vasitis nodosa (just a histologic dx, no pathology)
- ?PCa risk } likely a detection/referral bias

What is the management of rare non-motile sperm post-vasectomy?

- continue to use contraception until repeat S/A
- likely will become sterile } contraception is cautiously discontinued if persistent
- encourage more ejaculations

What is the management of rare MOTILE sperm post-vasectomy?

- likely failure at 3 months
- most will need repeat vasectomy

What are the options for post-vasectomy pain syndrome?

→ presents w/ orchialgia, pain w/ intercourse, pain w/ ejaculation, pain on exertion, tender epididymis

→ occurs 1 in 1000

- microsurgical denervation
- vas reversal
- open-ended vasectomy
- epididymectomy

What is involved in the work-up prior to vasectomy reversal?

→ **3-6% seek reversal**

- Hx and P/E } assess gap
 } assess testis size
 } look for evidence of sperm granuloma
- women to see gyne

What are the basic principles of vas reconstructive surgery?

- 1) mobilize both ends to prevent tension on anastomosis
- 2) preserve peri-vasal adventitia to keep arterial supply intact
- 3) precise approximation of cut lumens in watertight fashion
 - testicular side usually larger
 - prevent sperm granuloma and stricture

What different types of VV are described?

- 1) modified single layer VV
- 2) 2 layer VV (Jarvi, Lo)
- 3) multilayer VV
- 4) inguinal VV → especially with previous hernia repair
- 5) crossed VV → if contralateral vas is normal and contralateral testis is less functional

Describe a VV

- upper scrotal incision through dartos and then create sub-dartos pouch bluntly
- isolate and deliver vas with vas clamp then free vas without stripping perivascular adventitia
- locate vas on lateral side for VV (medial side for VE)
- identify healthy vas proximal and distal to vasectomy/obstruction
- cut vas with sharp blade after placing 5-0 PDS/propylene stay suture ~1cm from cut site
- identify sperm from testicular vas +/- saline vasogram of abdominal vas
- place vas clamp to approximate 2 ends
- close in 2 layer fashion (10-0 mucosa, 9-0 muscularis and adventitia)
- tie stay sutures on either end together to decrease tension on anastomosis

What maneuvers can be done to gain additional vasal length?

- separate vas from cord structures
- blunt finger dissection through external ring to free vas to internal ring
- dissect entire convoluted vas off attachments to epididymal tunica → gains 4-8cm
- dissect epididymis off testis → gains 4-8cm
- cut floor of inguinal canal and reroute vas under floor
- transposition of testis if crossed VV

What is the f/u post-VV?

- no heavy exertion for 2-3 weeks
- S/A in 1/12 then q3/12 } sperm usually seen 1-3 months post-VV
 } if no sperm by 6/12 then considered a failure

What are the potential complications of VV?

- 1) bleeding and hematoma
- 2) infection
- 3) 2° obstruction after successful VV (3-12%)
- 4) sperm granuloma

What are the success rates of VV?

- inguinal success rates lower than scrotal VV
- worse success rates w/ longer duration of obstruction & increasing F age (best if <3yrs & bad if >10yrs)
- better success rate if sperm granuloma
- ~85-95% patency rates → late obstruction in ~10-15%
- ~50% pregnancy rates

When should VE be considered?

- 1) prolonged period of obstruction → vasectomy >15yrs ago
→ 2° obstruction of epididymis is a time-related phenomenon
- 2) fluid from testicular vas is thick, pasty and devoid of sperm
- 3) fluid from testicular vas is creamy and contains debris and few sperm heads
(if few sperm heads/sperm parts, NOW CONSIDERED OK to do VV)
- 4) no fluid from testicular vas
- 5) irrigation of proximal vas fails to wash out sperm

Vasoe epididymostomy

What are the 3 variations of the microsurgical VE?

- 1) direct end-to-end } bloody due to cut end of epididymis
- 2) end-to-side } hard to place sutures
- 3) end-to-side intussusception } can't examine epididymal fluid prior to anastomosis setup

What are the findings suggestive of epididymal obstruction?

- azoospermia
- N palpable vas
- N hormone profile
- N-sized testes
- N semen volume
- palpably full or indurated epididymides

What are the causes of epididymal obstruction?

- 1) post-gonococcal epididymitis → rare now because of ABx
- 2) previous injury
- 3) congenital abnormalities b/w vas and epididymis (eg CF)
- 4) nonspecific inflammatory events
- 5) vasectomy → rare to see epididymal obstruction <4yrs post-vasectomy but 60% after 15yrs

What other features predict the likelihood of VV (not VE) at scrotal exploration?

- 1) presence of a sperm granuloma
- 2) long testicular vasal remnant (>2.7cm)

Describe a VE.

- GA (or continuous epidural anesthesia)
- vertical incision made in upper scrotum over each testis
→ can be extended into groin if more extensive mobilization of vas required
- can do open testis Bx if required +/- deliver testicle
- isolate vas on lateral side of cord for VE (medial for VV)
- vasostomy made at junction of straight and convoluted vas
- check distal lumen for patency → saline vasogram
- check testicular vas for fluid
- proximal end ligated or cauterized
- stay suture placed on distal vas (5-0 PDS/propylene)
- mobilize but don't strip vas from cord
- if more length required, can extend incision all the way to internal ring → open inguinal canal
- once adequate length obtained, microscope brought in
- anastomosis made at most distal, patent portion of epididymis
- different methods of anastomosis
 - 1) end-to-end → best for distal obstruction b/c tubule is larger & wall thicker in tail
 - 2) end-to-side → direct vs intussuscepted
 - less dissection
 - less bleeding b/c epididymis not transected
 - anastomosis made within tunica vaginalis

What are the potential complications of a VE?

- infection
- hematoma
- failed reconstruction
- testicular artery injury +/- testicular atrophy
- DVT from prolonged Sx

What are the success rates of VE?

- depends on } technique used
- } level of obstruction
- } age and reproductive capacity of female
- } surgeon skill
- ~75-80% patency rates
- ~40% pregnancy rates

What are the predictors of successful VV/VE?

- | | |
|-------------------------------------|--------------------|
| 1) patient factors | 2) partner factors |
| - obstruction <3yrs | - prior fertility |
| - med/surg hx post-vasectomy | - age <35yrs |
| - prior fertility | |
| - presence of sperm granuloma | |
| - long testicular remnant length | |
| - good quality sperm of vasal fluid | |
| - watery fluid at vasectomy site | |

SPERM RETRIEVAL

Vasal Aspiration of sperm

What is the role of vasal aspiration of sperm?

- option for men whose lack of ejaculation has a neurological cause
- use local anesthesia (esp if normal sensation eg anejaculation 2° to DM or MS)
- hemitranssect anterior wall of vas and aspirate fluid from testicular vas
- once adequate sperm obtained (confirm on micro) then vas closed with interrupted 9-0 suture
- sperm can be used for IUI or frozen for IVF/ICSI at later date

Epididymal Aspiration of sperm

What is the role of epididymal aspiration of sperm?

- 1) prior vasectomy with no wish for reversal
- 2) CBAVD

What are the methods of epididymal sperm aspiration?

→ taken from head of epididymis

- | | |
|---|---|
| 1) percutaneous (PESA) | 2) open microsurgical (MESA) |
| → for fresh or frozen IVF/ICSI | → for fresh or frozen IVF/ICSI |
| → quick, inexpensive | → requires OR, expensive |
| → can get insufficient sperm for cryo | → enables surgeon to collect large # of motile sperm for cryo |
| - esp if there's minimal dilation of head of epididymis | → open epididymal tunic & dilated tubule |
| → use local for cord block and skin | → 24 gauge angiocath used to aspirate fluid |
| → 25 gauge needle for aspiration | → 10-0 used to close tubule, 9-0 for tunic |
| | → ~60% pregnancy rates |

Open Testis Bx

*** Bx can be diagnostic and therapeutic where sperm is extracted for fresh or frozen IVF/ICSI ***
*** now mainly combined with therapeutic options ***

Testis Sperm Aspiration and Needle Bx

What are the pros and cons of testis needle aspiration of sperm (TESA)?

PROS	CONS
<ul style="list-style-type: none">- percutaneous under local (20 gauge)- cheap	<ul style="list-style-type: none">- can have inadequate sperm collection- may not aspirate from best tubules- often needs multiple Bx/aspirations

What is the role of non-microsurgical TESE?

- can take multiple mini-Bx specimens, being cautious to avoid major vessels and making only horizontal incisions into tunica albuginea
- 5-0 used to close

What is the role of microTESE?

- allows more meticulous opening of tunica albuginea, avoiding cutting across vessels critical to testis
- less tissue needs to be extracted and so more of testis is preserved
- higher rate of sperm retrieval for use with ICSI
- ~50% chance of finding sperm, 30% pregnancy rate

Describe a microTESE

- 15 blade used to incise down to tunical vaginalis, Metz used to cut into vaginalis sac
- testis delivered into field and under microscope
- horizontal (Schlegel) or vertical (Jarvi) incision made into tunica albuginea
- hemostasis of all small vessels at edge
- large, dilated, yellowish tubules sampled and examined on wet prep for sperm
- close tunica with interrupted 5-0 PDS/propylene
- close tunica vaginalis (infiltrate local anesthetic into sac – Jarvi)
- close dartos muscle with 2-0 chromic
- subcuticular 4-0 vicryl

Which patients generally have smaller seminiferous tubules?

- SCOS
- sclerosis associated with Klinefelter's syndrome
- testicular atrophy
- UDT
- prior orchitis

SURGICAL MANAGEMENT OF EJACULATORY DUCT OBSTRUCTION

What are the causes of ejaculatory duct obstruction?

- 1-5% of infertile men
- congenital → utricular, Mullerian, Wolffian duct cyst
→ congenital atresia/stenosis of ejaculatory duct
- acquired → infection
→ trauma
→ calculus formation
→ cyst formation after instrumentation

Diagnosis

When is ejaculatory duct obstruction suspected?

- 1) azoospermia
- 2) decreased ejaculate volume (<1mL)
- 3) acidic pH
- 4) fructose negative
- 5) normal hormone profile
- 6) dilated SV's or midline mass on DRE

When is partial ejaculatory duct obstruction suspected?

- difficult to Dx
- very low motility w/ oligospermia } sperm stasis + higher temp at site of obstruction decreases sperm motility
- normal-sized testes
- normal hormone profile
- TRUS recommended in this setting

How is ejaculatory duct obstruction diagnosed?

- 1) static tests
 - TRUS } pt in decubitus position
 } cystic midline structure or SV **>1.5cm axial diameter**
 - MRI
 - SV aspiration } alternative to vasography to Dx distal vasal obstruction
 - } get pt to ejaculate day prior, fleet, Abx
 - } TRUS guidance used to aspirate SV
 - } **>3 motile sperm/hpf is diagnostic of ED obstruction**
 - means at least 1 vas and epididymis is open
 - } if no sperm, do testis Bx to confirm spermatogenesis
 - } if ED obstruction + epididymal obstruction, fix ED obstruction first then decide on VE (depends on presence of sperm)
 - may need MESA + cryo for IVF/ICSI
- 2) dynamic tests
 - vasography } usually reserved for when TRUS is equivocal or no sperm found on SV aspirate
 - } can cause vasal injury and occlusion
 - seminal vesiculography } injection of indigo carmine or methylene blue transrectally in SV
 - } can help assess feasibility of TURED and can also guide resection of ED @ time of TURED

How is vasography performed?

- fine needle vasography → technically difficult (30 gauge angiocath needle)
→ hard to get sufficient vasal sperm for cryo
- open vasostomy → testis delivered via high scrotal incision
→ incise vasal sheath longitudinally to preserve vasal vessels
→ hemitranssect vas
→ check testicular vas for fluid and sperm to r/o proximal obstruction
→ check first w/ saline vasography } if easy & no resistance, no need for contrast
→ use only indigo carmine } DO NOT USE methylene blue (impairs sperm motility)
→ Foley placed to identify BN } air in balloon
→ dye seen in urine confirms patency
→ can also pass 1-0 prolene to measure site of obstruction

What are the potential complications of vasography?

- more common with fine needle vasography
- hematoma
- stricture
- sperm granuloma
- vascular injury to vas deferens

Treatment

What are the treatment options for ejaculatory duct obstruction?

- 1) TURED
 - primary treatment modality
 - resection of veru } ED cyst is usually deep and just posterior to veru
 - can use real-time TRUS to guide resection
 - done when you see copious cloudy material or indigo carmine
 - if cyst still not unroofed, can use Collins knife to make B/L incisions just lateral to base of resected veru
 - Foley overnight
- 2) transurethral balloon dilatation of ejaculatory duct
 - partial resection of veru
 - ED cannulated and dilated with 4mm wide, 2cm long balloon
 - good for extraprostatic or partial obstruction of ED

What are the potential complications after TURED?

- reflux of urine into ED, SV, vas and epididymis } can lead to acute or chronic epididymitis
} can also worsen sperm motility
- BN injury } can cause retrograde ejaculation
- EUS injury } incontinence
- rectourethral fistula
- post-op bleeding
- BN contractures

What are the success rates of TURED?

- ~50% improvement in semen parameters
- ~30% pregnancy rate
- better outcome if:
 - partial obstruction
 - midline cysts causing obstruction
 - congenital obstruction

What are the management options for ED obstruction with secondary epididymal obstruction?

- epididymal sperm aspiration for cryo + IVF/IVSI
- simultaneous TURED + VE rarely successful

TREATMENT OF ANATOMIC, CONGENITAL, AND ORGANIC CAUSES OF INFERTILITY

Hypospadias Repair

What are the management options for infertility due to hypospadias?

- IUI
- surgical correction
- *** hypospadias has been associated with abnormal sperm parameters (morphology) and endogenous endocrine abnormalities in the fathers of hypospadiacs ***

Plication for Peyronie's Disease

What are the management options for infertility due to Peyronie's disease?

- wait at least 1 yr for plaques to stabilize
- conservative management with resolution only seen in ~15%
 - less likely if calcifications in plaques, curvature >45 degrees, symptoms >2yrs and associated Dupuytren's contractures
- surgical treatment:
 - a) penile shortening procedures
 - eg Nesbit
 - b) penile lengthening procedures
 - eg excision/incision + grafting
 - c) penile prosthesis implantation
 - only when concomitant ED present
 - prosthesis inserted & inflated, then plaque is incised and patched or penis is bent in the opposite direction to break plaque ("modeling")

Erectile Dysfunction

What are the management options for infertility due to ED?

- complete impotence seen in ~15% among men 70 yrs and older, but 5% in men in 40's
- medical vs surgical management

Ejaculatory Dysfunction

How common is ejaculatory dysfunction?

- represents ~2% of infertile men

What are the causes for retrograde ejaculation

- due to lack of sympathetically driven BN closure
- 1) RPLND (most common)
- 2) DM
- 3) bladder neck surgery or TURP
- 4) unknown trauma
- 5) medications
- 6) urethral strictures
- 7) SCI

What are the management options for retrograde ejaculation?

- medical
 - **α agonists** (pseudoephedrine, ephedrine, milodrin)
 - sympathomimetics (**imipramine**)
 - antihistamines (brompheniramine)
- retrieval of sperm from post-ejaculate urine
 - make urine alkalinized first (K citrate)
 - can be used for IUI or IVF

What are the causes of anejaculation?

- 1) nerve damage
 - RPLND
- 2) neurologic disease
 - SCI (most common), DM, MS
- 3) psychogenic

When should a diagnosis of anejaculation be suspected?

- complete absence of antegrade ejaculation
- fructose-negative, sperm-negative post-orgasmic urine

What are the management options for anejaculation?

- 1) medical → α agonists
 - bupropion (wellbutrin)
- 2) penile vibratory stimulation → place on frenulum
 - need to have intact ejaculatory reflex arc
 - **good only for SCI above T10**
- 3) electroejaculation → rectal probe stimulates perirectal, periprostatic sympathetic nerves
 - GA required if no SCI or incomplete SCI
 - watch out for autonomic dysreflexia } 10-30mg nifedipine SL
 - Sudafed + K citrate + fleet enema
 - empty bladder with Foley prior (mineral oil only)
 - process antegrade and retrograde samples separately
- 4) vasal sperm aspiration

What are the advantages of penile vibratory stimulation over electroejaculation?

- for lesions above T10
- doesn't need GA
- cheaper
- sperm obtained has better motility, viability, ability to penetrate cervical mucous, and better fertilizing capacity
- higher pregnancy rates
 - 47% (PVS + ICSI) vs 29% (electro + ICSI)

What are the indications for genetic testing in azoospermic men?

- ## IN VITRO FERTILIZATION WITH INTRACYTOPLASMIC SPERM INJECTION

- oocytes retrieved after stimulation under sedation or GA
- viable sperm injected directly into oocyte after sperm tail immobilized
- embryos that cleave and continue to develop are transferred to uterus transvaginally 3-5 days after fertilization } recommend transfer of 2-4 embryos
- ~70% fertilization rates
- **delivery rate per retrieval is ~50%**
- fetal abnormalities double natural conception (3.2% vs 1.6%)

Chapter #21 – Erections

PHYSIOLOGY OF PENILE ERECTIONS

What are the branches of the Internal pudendal artery (terminal branch of internal iliac)?

→ IPP BP/CP

- 1) Inferior rectal artery
- 2) Perineal artery
- 3) Posterior scrotal (posterior labial)
- 4) artery of Bulb of Penis
- 5) Common Penile artery → dorsal + cavernosal + bulbourethral

Describe the gross anatomy of the penis

- corpora cavernosum join beneath pubis to form body of penis
 - incomplete septum distally
 - enclosed by tunica albuginea (outer longitudinal & inner circular fibers)
 - smooth muscle bundles w/in
- distal to bulb, corpus spongiosum tapers & runs on ventral surface of cavernosa, expanding to form glans
 - urethra runs along entire length, starting at perineal membrane
 - urethra is lined proximally by columnar, distally by squamous epithelium
 - may see mucous-secreting glands of Littre
- Buck's fascia surrounds cavernosal bodies and splits to surround spongiosum ventrally
 - fuses with pubis via suspensory ligament
 - distally it fuses with glans at corona
 - **proximally in perineum it fuses with tunica albuginea and surrounds crura and bulb of spongiosum**
 - penile fracture tears tunica albuginea → contained by Buck's so ecchymosis limited to shaft
 - neurovascular bundles of penis lie DEEP to Buck's fascia
- **penile skin** is highly elastic and without appendages (hair or glandular elements)
 - **blood supply is independent of the erectile bodies and comes from the external pudendal branches of femoral vessels**
 - rich anastomotic network so penile skin is ideal for mobilization on vascular pedicle

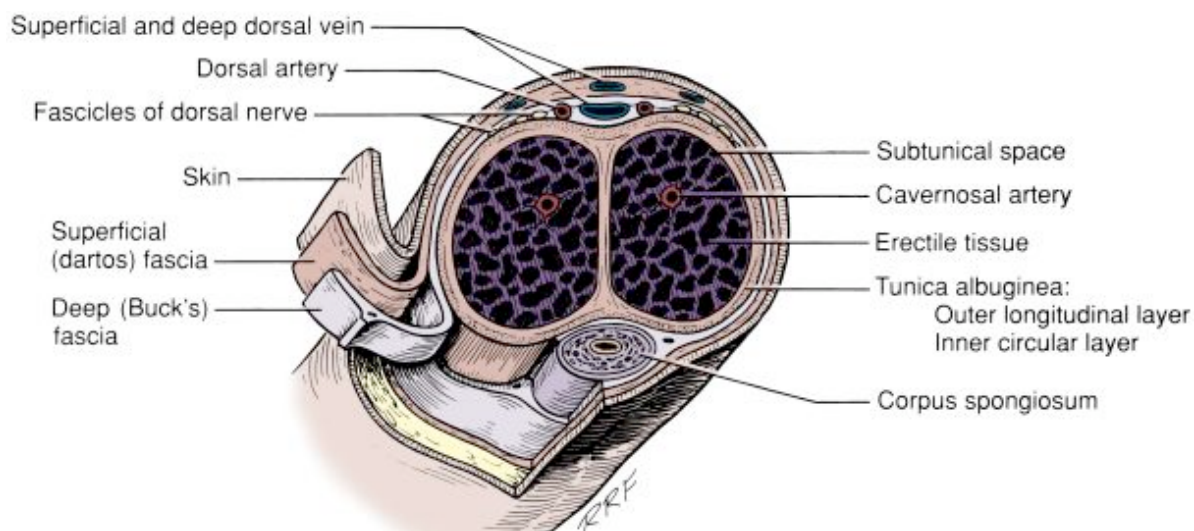
What are the layers of tissue surrounding the penis?

- penile skin
- dartos fascia } continuous with Scarpa's fascia
- tela subfascialis → very thin CT layer
- Buck's fascia } continuous with external spermatic fascia
- tunica albuginea

What are the glands of Tyson?

- preputial glands at coronal sulcus that secrete sebaceous material (smegma when mixed with desquamated epithelial cells)

▪ Corpora cavernosa	Support corpus spongiosum and glans
▪ Tunica albuginea (of corpora cavernosa)	Contains and protects erectile tissue Promotes rigidity of the corpora cavernosa Participates in veno-occlusive mechanism
▪ Smooth muscle	Regulates blood flow into and out of the sinusoids
▪ Ischiocavernosus muscle	Pumps blood distally to hasten erection Provides additional penile rigidity during rigid erection phase
▪ Bulbocavernosus muscle	Compresses the bulb to help expel semen
▪ Corpus spongiosum	Pressurizes and constricts the urethra lumen to allow forceful expulsion of semen
▪ Glans	Acts as a cushion to lessen the impact of the penis on female organs Provides sensory input to facilitate erection and enhance pleasure Facilitates intromission because of its cone shape



What is the blood supply to the penis?

- penile skin } **external pudendal** branch off femoral vessels
- penis } int. iliac → int. pudendal → common penile
 - 1) **dorsal** → cavernous branches to corpora & circumflex branches to spongiosum & urethra (ends in glans)
 - 2) **cavernosal** → straight and helicine arteries to cavernosum
 - 3) **bulbourethral** → spongiosum, urethra, & glans
- } accessory pudendal artery may also contribute
- } other possible accessory arteries → from ext. iliac, obturator, vesical and femoral

What is the venous drainage of the penis?

- all 3 systems can communicate
- 1) superficial (skin)
 - **superficial dorsal vein** → usually drains to **L saphenous vein**
- 2) intermediate
 - subtunical capillary plexus → emissary veins → circumflex veins → **deep dorsal veins** (w/in Bucks) + periurethral veins → **Santorini's plexus** → vesical plexus → **internal iliacs** veins
- 3) deep
 - **crural, cavernosal, bulbar veins** → **internal pudendal veins** → internal iliac veins

What is the average size of the penis?

- flaccid length is 8-9cm
- stretched or erect length is 12-14cm

What are the 2 layers of the tunica albuginea covering the corpora cavernosa?

→ composed of fibrillar collagen (mostly type 1 and some type 3) + elastin

- inner circular layer } support
 - } intracavernous pillars radiate from inner layer to support
 - } emissary veins run b/w inner & outer layer, often piercing inner layer obliquely
- outer longitudinal layer } strength layer
 - } extends from glans to proximal crura, inserting into inferior pubic rami
 - } absent between 5 and 7 o'clock (ventral groove)
 - weakest area of tunica
 - } compresses emissary veins during erection
 - corpus spongiosum lacks intracorporeal struts and outer layer

What are the 2 ligamentous supports of the penis?

- 1) fundiform ligament } arises from **Colles' fascia**
 - } lateral, superficial, and **NOT stuck to tunica albuginea**
- 2) suspensory ligament } arises from **Buck's fascia**
 - } 2 lateral bundles + 1 median bundle and **stuck to tunica**
 - attaches tunica albuginea of corpora cavernosa to pubis

How does the structure of the corpus spongiosum differ from the corpora cavernosa?

- larger sinusoids
- thinner tunica (only inner circular layer)

What are the anatomic changes associated with erections?

→ **sinusoidal relaxation + arterial dilation + venous compression**

- 1) relaxation of smooth muscle
- 2) dilation of arterioles & arteries by increased blood flow in both diastolic & systolic phases
- 3) trapping of incoming blood by the expanding sinusoids
- 4) compression of subtunical venous plexuses between tunica albuginea & peripheral sinusoids
 - reduces venous outflow
- 5) stretching of tunica to its capacity
 - occludes emissary veins b/w inner circular & outer longitudinal layers, further ↓'ing outflow
- 6) increase in PO₂ (to ~90 mmHg) & intracavernous pressure (~100 mmHg)
 - raises penis to full-erection phase
- 7) pressure ↑'s more (to several hundred mmHg) w/ ctx of ischiocavernosus m. (rigid-erection phase)

What are the 3 phases of detumescence?

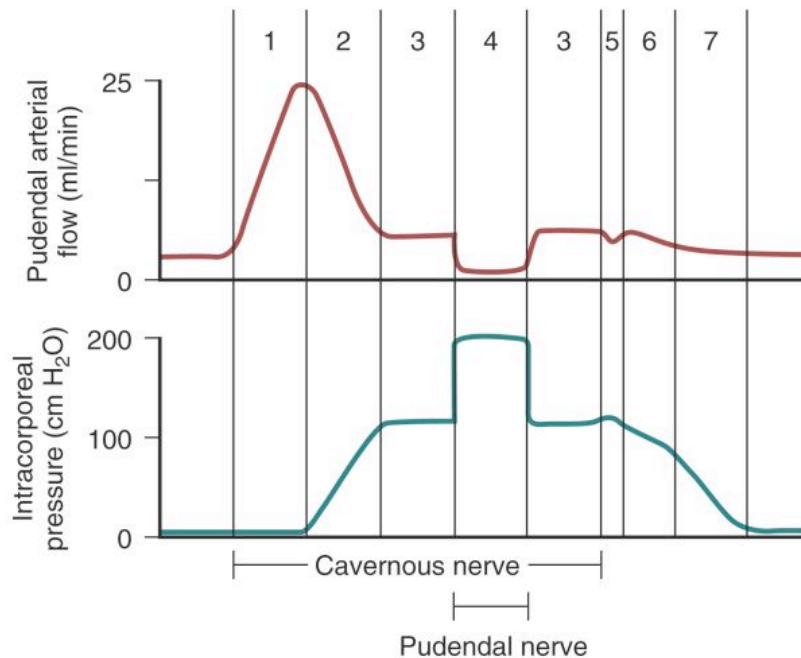
- 1) transient intracorporeal pressure increase } start of smooth muscle contraction
- 2) slow pressure ↓ } slow reopening of venous channels + resumption of basal level of arterial flow
- 3) fast pressure ↓ } fully restored venous outflow capacity

What are the 7 phases of penile erection & detumescence?

- 1) latent } dilation of arteries, sinusoidal relaxation and trapping of blood
- 2) tumescence } compression of subtunical venous plexuses, stretching of tunica to capacity
- 3) full erection } increase in IC pressure
- 4) rigid erection } contraction of ischiocavernosus muscle
- 5) initial detumescence } smooth muscle contraction against closed venous system
 - } transient rise in IC pressure
- 6) slow detumescence } slow reopening of venous channels
- 7) fast detumescence } fully restored venous outflow capacity

How does the hemodynamics of the corpus spongiosum differ from the corpora cavernosa?

- pressure is only 1/3 to 1/2 that in the corpora cavernosa
→ thinner tunica albuginea over spongiosum and virtually absent over the glans
- contraction of ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, resulting in increased pressure of spongiosum + glans



What is the innervation of the penis?

- **somatics } pudendal nerve (S2-S4)**
 - inferior rectal, dorsal penile, perineal branches
 - dorsal penile nerves provide sensation to penis
 - follow dorsal arteries and richly supply glans
 - **run outside pelvis ∴ preserved during pelvic sx**
 - perineal nerve branches supply ventral penis
 - also controls contraction of ischiocavernosus (rigid-erection phase) and bulbocavernosus (ejaculation) muscles
 - **autonomics } cavernosal nerves** innervate corporal bodies (NVB)
 - come **from pelvic plexus** and enter corporal bodies
 - **sympathetic tone (T10-L2)** causes detumescence
 - **parasympathetic activity (S2-S4)** causes erections
 - release NO, acetylcholine, VIP that causes smooth muscle and arterial relaxation
- } dorsal penile nerve may also have some parasympathetic input

What is the center of somatomotor penile innervation in the spine?

- Onuf's nucleus (S2-S4)

What are the 3 main types of erections?

- 1) psychogenic } from audiovisual stimuli or fantasies
 } brain modulates spinal erection centres (T11-L2 and S2-S4)
- 2) reflexogenic } from tactile stimulation of genitals (S2-S4)
 } some sensory info to brain but also direct autonomic activation of cavernous nerves for erections
- 3) nocturnal } occurs during REM and associated with testosterone levels

What are the effects of SCI on erections?

- sacral SCI } NO reflexogenic erections but YES psychogenic erections
 → cerebral impulses travel via sympathetics (T11-L2)
 → weaker erections though
- lesion above T9 } YES reflexogenic erections but NO psychogenic erections

Which spinal reflexes are elicited with stimulation of penile dorsal nerve (somatic + ?parasympathetic)?

Stimulation	spinal centre	efferent	effect
noxious, abrupt stimulation OR low-intensity continuous	sacral motor + sacral parasymp's	pudendal nerve (motor) + 1) pelvic nerves 2) cavernous nerves	bulbocavernous reflex + 1) bladder inhibition and BN closure 2) penile erections
high-intensity continuous	1) sacral motor & parasympathetics 2) TL sympathetics	pudendal, pelvic, and cavernous nerves	ejaculation

Which supraspinal brain centres are involved in sexual function (CHART)?

Level	Region	Function
forebrain	- medial amygdala - stria terminalis - pyriform cortex - hippocampus - R insula + inferior frontal cortex - L anterior cingulate cortex	- controls sex drive - inhibits sex drive - erections - sexual arousal
hypothalamus	- medial preoptic area (MPOA) - paraventricular nucleus (PVN)	- recognition of sexual partner - erections
brain stem	- nucleus paragigantocellularis - A5-catecholaminergic cell group - locus ceruleus	- inhibits erections - innervates perineal muscles
midbrain	- periaqueductal gray	- relay centre for sexual stimuli

What are the 3 factors involved in maintenance of flaccidity?

- 1) intrinsic myogenic activity of smooth muscles
- 2) adrenergic neurotransmitters
 - **NE** } **principle neurotransmitter**
 - } α -adrenergic receptors >>> β -adrenergic receptors
- 3) endothelin-derived contracting factors } elevated intracellular Ca
 - **endothelin** } most potent vasoconstrictor
 - } mediated by ETA and ETB receptors
 - } involves degradation of inositol phosphate (IP) & activation of protein kinase C
 - **prostaglandins (PGF2 α)**
 - AT II
 - TXA2

What are the 3 factors responsible for detumescence?

- 1) cessation of NO release
- 2) breakdown of cGMP by PDE
- 3) sympathetic upregulation with ejaculation

What peripheral neurotransmitters are involved in erections?

- 1) NO } principle neurotransmitter
 - from non-adrenergic, non-cholinergic (NANC) neurotransmission & from endothelium
 - **binds to guanylyl cyclase and ↑'s production of cGMP**
 - ↓'d intracellular Ca results in relaxation of smooth muscle via PK G
 - **neuronal NOS (nNOS) = NO that initiates smooth muscle relaxation**
 - **endothelial NOS (eNOS) = NO that maintains erections**
- 2) acetylcholine } minor role
- 3) PGs } **PGE1 is pro-erectile via adenylyl cyclase**
- 4) VIP

What central neurotransmitters are involved in erections?

- | | |
|---|---|
| → +ve effects on erections/sex drive | → - ve effects on erections/sex drive |
| <ol style="list-style-type: none">1) dopamine } D1 and D2 receptors2) NE3) oxytocin4) NO5) melanocortins6) serotonin (5-HT1) | <ol style="list-style-type: none">1) prolactin2) opioids3) GABA4) serotonin (5-HT2, 5-HT3) |

What factors increase or decrease NOS levels?

- | | |
|--|---|
| → increase | → decrease |
| <ul style="list-style-type: none">- oxygen- androgens- L-arginine- PGE1 | <ul style="list-style-type: none">- castration- denervation- DM- increased cholesterol |

What is the role of intracellular Ca on erections?

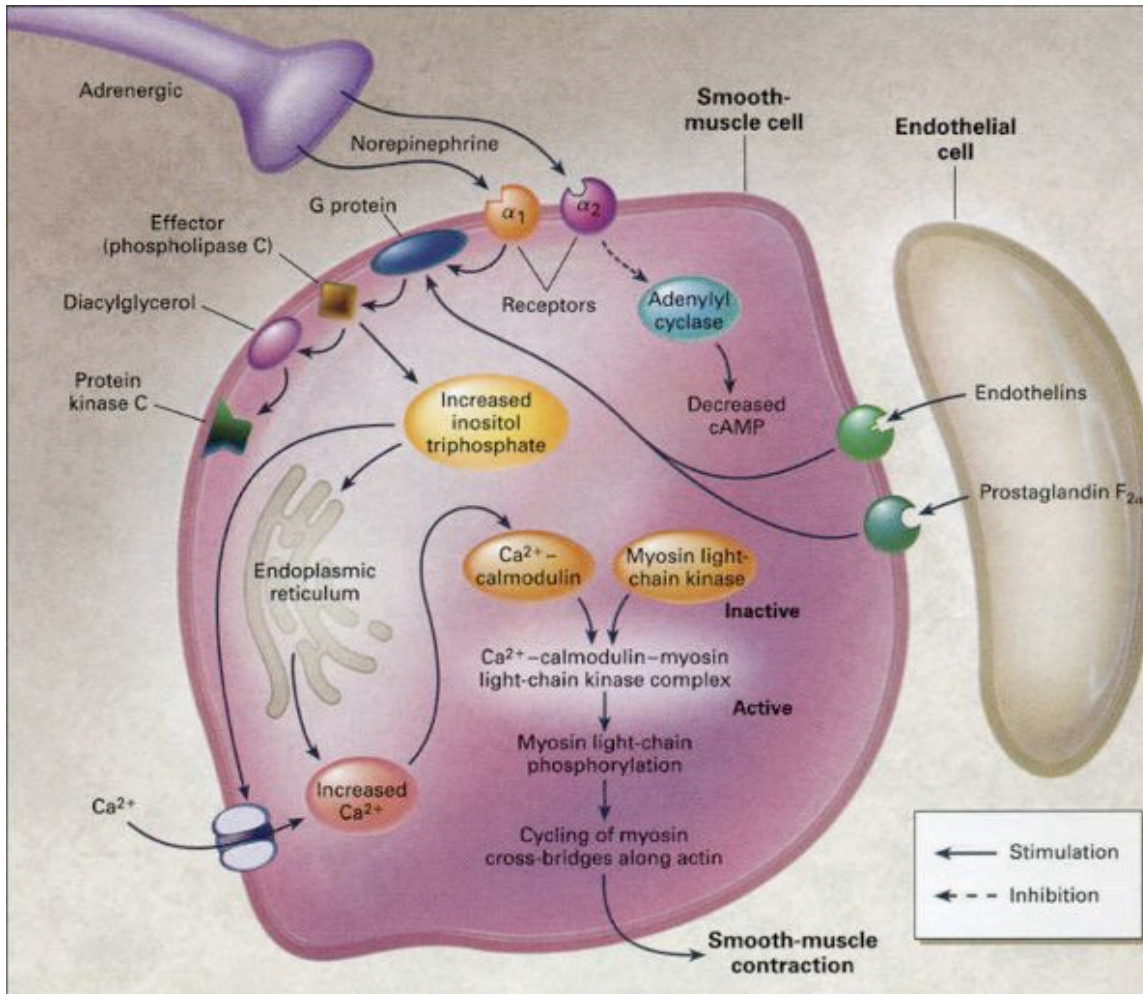
- flaccidity
 - NE + endothelin-derived factors (endothelin, PGF2 α , etc) result in elevated intracellular Ca
 - ↑'d intracellular Ca results in increased smooth muscle tone
- erections
 - NO, etc increase cGMP and cAMP activity
 - **cGMP and cAMP then activates protein kinases resulting in**
 - 1) opening of K channels + hyperpolarization
 - 2) sequestration of intracellular Ca into ER
 - 3) blockage of Ca influx by inhibition of voltage-gated Ca channels
 - **↓'d levels of intracellular Ca results in smooth muscle relaxation**

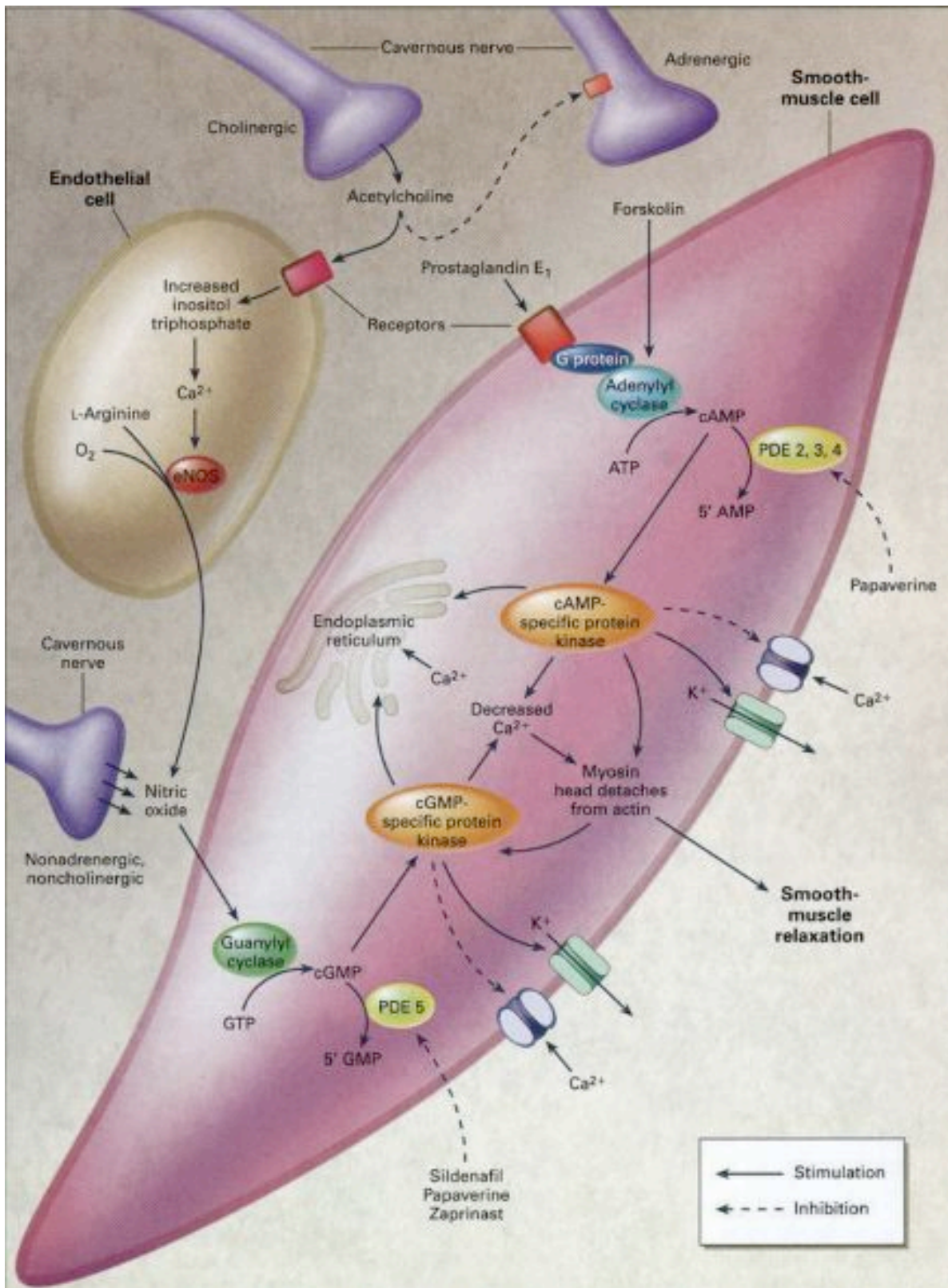
What is phosphodiesterase (PDE)?

- enzyme that catalyzes the hydrolysis of cGMP and cAMP
- consists of 11 subtypes } encoded by 21 distinct genes
 - } all types of PDE have been found in corpus cavernosum
 - EXCEPT PDE6 (photoreceptor cells)**
 - side effect of Viagra (blue hue)
 - } **PDE5 is the main phosphodiesterase in the penis responsible for breakdown of cGMP**
 - } PDE11 found in skeletal muscle
 - side effect of cialis (back pain)
- **papaverine inhibits PDE2, PDE3, PDE4, PDE5**

What are the 4 main K⁺ channel subtypes found in cavernous smooth muscle?

- 1) Ca-sensitive maxi-K
- 2) metabolically regulated KATP
- 3) delayed rectifier
- 4) fast transient A current





→ MOLECULAR MECHANISM OF PENILE SMOOTH MUSCLE RELAXATION

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

How common is ED?

- Massachusetts Male Aging Study } 1700 men
 - between 40 and 70yrs, the probability of complete ED increases from 5% to 15%, moderate ED increases from 15% to 35%, and mild ED remains constant at 15%
 - increased incidence of ED associated with DM, heart disease, HTN
- <10% of men <40yrs, 10-30% for men 40-60yrs, 20-40% for men 60-70yrs & 40-70% for men >70yrs

What are the main RFs for ED?

- poor general health status
- psychiatric or psychologic disorders
- DM
- chronic disease (renal failure, liver failure, etc)
- cardiovascular RFs (CAD, HTN, PVD)
- smoking
- medications
- low testosterone states
- concurrent other GU disease

What is the ISIR classification of ED (CHART)?

→ International Society of Impotence Research

1) Organic

- vasculogenic } arteriogenic (arterial, arteriolar)
 - } cavernosal (tunica albuginea, cavernous smooth muscle, endothelium, emissary vein, gap junction, fibroelastic trabeculae)
 - } mixed
- neurogenic } central, spinal, peripheral
- anatomic
- endocrinologic (testicular, pituitary, thyroid)

2) psychogenic

- generalized } unresponsiveness
 - primary lack of sexual arousability
 - aging-related decline in sexual arousability
- } inhibition
 - chronic disorder of sexual intimacy
- situational } partner-related
 - lack of arousability in specific relationship
 - lack of arousability owing to sexual object preference
 - high central inhibition owing to partner conflict or threat
- } performance-related
 - associated with other sexual dysfunction (eg rapid ejaculation)
 - situational performance anxiety (eg fear of failure)
- } psychological distress- or adjustment-related
 - associated with negative mood state (eg depression) or major life stress (eg death of partner)

*** **most cases of ED are mixed etiology** ***

What are the 2 main mechanisms responsible for psychogenic ED?

- 1) direct inhibition of spinal erection centre by brain
 - exaggeration of N suprasacral inhibition
- 2) excessive sympathetic outflow or elevated peripheral catecholamine levels
 - increase in penile smooth muscle tone to prevent relaxation

What are the 3 main integration centres for sex drive & erection in the brain?

- MPOA (hypothalamus)
- PVN (hypothalamus)
- hippocampus

What are the causes of neurogenic ED?

→ central

- Parkinson's disease
- stroke
- encephalitis
- temporal lobe epilepsy
- tumours
- dementia +/- alzheimer's
- Shy-Drager syndrome
- trauma

→ spinal

- trauma
- syringomyelia
- tumour
- spina bifida
- transverse myelitis
- MS

→ peripheral

- iatrogenic
- trauma
- peripheral neuropathy

What is the effect of SCI on erections?

- depends on location & nature of injury
- can also impair ejaculation and orgasm

→ **complete upper cord } YES reflexogenic erections but NO psychogenic erections**

→ **complete lower cord } NO reflexogenic erections (rare) but YES psychogenic erections**

What are the effects of testosterone on sexual function?

- 1) enhances sexual interest
- 2) increases frequency of sexual acts
- 3) increases frequency of nocturnal erections (little effect on visual/fantasy-induced erections)

How does hyperprolactinemia affect sexual function?

- loss of libido (inhibits dopamine at MPOA)
- ED
- gynecomastia
- galactorrhea
- infertility
- decreased levels of T and TSH

What are some RFs for ED due to arterial insufficiency?

- HTN
- hyperlipidemia
- smoking
- DM
- pelvic RADs
- blunt perineal or pelvic trauma (common penile/cavernous a.)
- long-distance cycling

What are the mechanisms of vasculogenic ED?

- 1) structural changes
 - decreased oxygen tension } less smooth muscle content + diffuse venous leakage
- 2) vasoconstriction
 - increased basal tone + enhanced sympathetic activity + vascular wall hypertrophy
- 3) impaired endothelium-dependent vasodilation
 - decreases acetylcholine-induced vasorelaxation

What are the causes of venogenic ED (veno-occlusive dysfunction)?

- 1) degenerative tunical changes \ Peyronie's, DM, old age
- 2) fibroelastic structural alterations / penile fracture, etc
- 3) insufficient trabecular smooth muscle relaxation } excessive adrenergic tone, decreased NO
- 4) venous shunts } trauma, iatrogenic

Which medications can induce ED? } “7A’s CHOP Dick”

- 1) Anti-hypertensives } diuretics
 } non-selective β -blockers (eg propranolol, guanethidine)
 $\rightarrow \alpha_1$ -blockers and ARBs actually improve erectile function
 \rightarrow ACEI and CCB have no effect
 - 2) **α -agonists** } clonidine, methyldopa
 - 3) Anti-psychotics } resperidone, clozapine
 \rightarrow decreased dopamine (increases prolactin), β -blockade
 \rightarrow older “typicals” worse for EPS
 - 4) Anti-depressants } TCA (peripheral anticholinergic + β -adrenergic effects)
 } MAO inhibitors (orgasmic dysfunction by unclear mechanism)
 } SSRIs eg paroxetine (increased serotonin 5-HT₂, 5-HT₃, decreased dopamine)
 - 5) Anxiolytics } benzo's (upregulate GABA, decreased dopamine)
 \rightarrow trazodone (priapism risk) works by up-regulating 5-HT₁ (pro-erectile)
 - 6) Anti-androgens } 5ARIs, nonsteroidal anti-androgens (flutamide, bicalutamide), steroidal
 anti-androgens (cyproterone), LHRH agonists
 - 7) Alcohol abuse + tobacco
 - 8) others (“CHOP Dick”) } Chemo, H₂-blockers (cimetidine), Opiates, Protease inhibitors, Digoxin, etc
- *** statins NOT associated with ED ***

What are the effects of aging on erectile function?

- likely an effect on endothelial NO (important in maintaining erections)
- greater latency to erection
- less turgidity
- loss of forceful ejaculation
- decreased ejaculate volume
- longer refractory period
- decreased frequency and duration of nocturnal erections

What are the effects of DM on erectile function?

- vasculogenic
 - 1) more atheromatic lesions in large vessels and stenosis in pudendal and iliac arteries
 - 2) higher prevalence of penile arterial insufficiency on duplex U/S
 - 3) lower penile rigidity after ICI of vasodilators
- neurogenic
 - 4) peripheral neuropathy
- endocrine
 - 5) decreased nocturnal erections
- structural/anatomic
 - 6) decreased smooth muscle content
 - 7) loss of endothelial cell function (decreased NO synthesis)
 - 8) increased endothelin B receptor binding sites and ultrastructural changes
 - 9) increased oxygen free radicals and oxidative stress injury
 - 10) increased levels of glycosylated end products

How does renal failure cause ED? } } } “PAPA Has ED”

- mainly the effects of **persistent uremia**
- **Psychologic** factors
- **Atherosclerosis** accelerated
- **Prolactin** elevated
- **Autonomic neuropathy**
- **Hypothalamus-pituitary-testis** axis abnormalities
- **Endothelial Dysfunction** causing ↓'d NO bioavailability

Management of ED in renal failure

Medical	Surgical
1) optimize general condition a) atherosclerotic risk factors b) ED-inducing drugs c) adequate dialysis 2) Viagra – ↓ dose a) renal dosing: start 25 mg od b) cyclosporine: start 25 mg od	1) transplant: returns 80% of pts to pre-failure potency 2) semi-rigid prosthesis: a) more reliable (↓ re-operation rate) b) no peri-vesical reservoir to get in way of transplant 3) inflatable prosthesis a) use a scrotal reservoir

What are the causes of primary ED?

→ lifelong inability to initiate or maintain erections

1) **psychogenic (majority)**

2) organic } less common

} congenital malformation leading to neurologic, arterial, & veno-occlusive dysfxn

} endocrine cause uncommon (low sex drive is usually main symptom)

→ can lead to micropenis, hypospadias, epidspadias, etc

OTHER

What are the causes of male anorgasmia?

→ **much more common in F**

→ primary

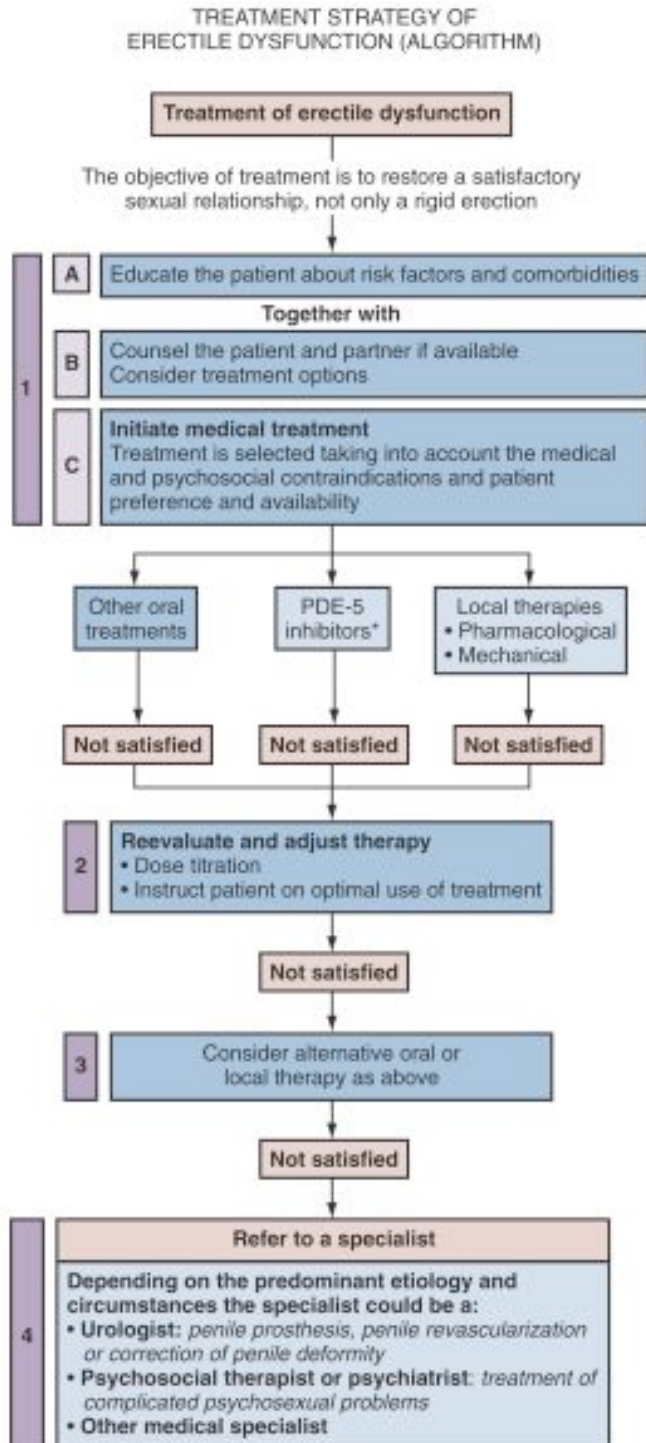
- idiopathic \ extremely rare
- psychiatric / in males

→ secondary

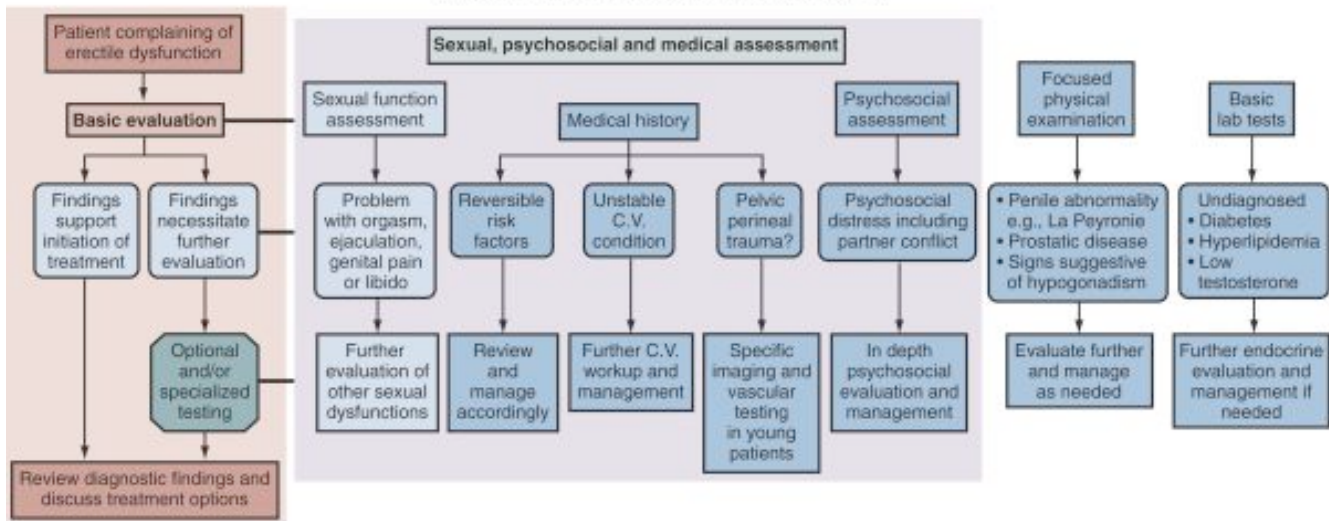
- psychiatric (eg depression) } **most common cause**
- DM neuropathy
- Multiple Sclerosis
- SCI
- genital mutilation
- pelvic trauma
- EtOH'ism
- CV disease
- meds (eg SSRIs)
- post-RP

Chapter #22 – ED and Premature Ejaculation

PATIENT-CENTERED EVALUATION



ALGORITHM FOR DIAGNOSTIC EVALUATION OF ED



What are some of the commonly referenced questionnaires used to assess sexual function?

- 1) IIEF } International Index of Erectile Function
- 2) SHIM } Sexual Health Inventory for Men
- 3) BMSFI } Brief Male Sexual Function Inventory
 - sex drive (2 items), erections (3 items), ejaculation (2 items), perception of problems (3 items), overall satisfaction (1 item)
- 4) EDITS } Dysfunctional Inventory for Treatment Satisfaction
 - good for drug studies
- 5) Male Sexual Function Scale } from 2nd ICSD
 - desire, erection, ejaculation, satisfaction

What is the IIEF-15?

- most widely used & statistically validated in many languages
- 15 items total with 5 domains:
 - 1) **sexual desire**
 - 2) **erectile function**
 - 3) **intercourse satisfaction**
 - 4) **orgasmic function**
 - 5) **overall satisfaction**
- total score **out of 75** (minimum is 5)
- measures over the **past 4 weeks**

What is the IIEF-5?

- shorter 5 item version of IIEF-15 looking mainly at erectile function
- 4 items from erectile function domain + 1 item from sexual intercourse satisfaction domain
- total score out of 25 (minimum is 5)
 - } 22 to 25 = no ED
 - } 17 to 21 = mild ED
 - } 12 to 16 = mild to moderate ED
 - } 8 to 11 = moderate ED
 - } 5 to 7 = severe ED
- IIEF-5 measures **over past 6 months**

What is the ISIR classification of ED?

→ International Society of Impotence Research

1) Organic

- vasculogenic } arteriogenic (arterial, arteriolar)
 - } cavernosal (tunica albuginea, cavernous smooth muscle, endothelium, emissary vein, gap junction, fibroelastic trabeculae)
 - } mixed

→ neurogenic } central, peripheral (sensory, motor, autonomic, neurotransmitters)

→ anatomic } Peyronie's, etc

→ endocrinologic (testicular, pituitary, thyroid)

2) psychogenic

→ generalized } unresponsiveness

- primary lack of sexual arousability
- aging-related decline in sexual arousability

} inhibition

- chronic disorder of sexual intimacy

→ situational } partner-related

- lack of arousability in specific relationship
- lack of arousability owing to sexual object preference
- high central inhibition owing to partner conflict or threat

} performance-related

- associated with other sexual dysfunction (eg rapid ejaculation)
- situational performance anxiety (eg fear of failure)

} psychological distress- or adjustment-related

- associated w/ negative mood state (eg depression) or major life stress (eg death of partner)

*** most cases of ED are mixed etiology ***

What are the RFs for organic ED?

- older age
- HTN
- smoking
- CAD
- PVD
- DM
- hypercholesterolemia
- medications
- pelvic trauma/surgery
- chronic disease (renal failure, liver failure, etc)

What features on history suggest a psychogenic cause of ED (CHART)?

- acute onset
- situational ED
- variable course
- rigid non-coital erections
- long history of psychosexual problems
- primary anxiety and fear

What is involved in the initial evaluation of ED?

1) History

- must assess 3 main domains for any sexual problem } erections, orgasm, ejaculation
- CC } obtaining, maintaining, satisfaction, onset, duration, pain, nocturnal erections
- IIEF-5 questionnaire (score out of 25), EDITS, BMSFI
- sexual hx } situational, interest/libido, satisfaction, sexual orientation, premature ejaculation, nocturnal erections, pain, masturbation, previous Rx
- PMHx } atherosclerosis, CAD, PVD, HTN, cholesterol, DM, anxiety, depression, psych hx, pelvic/perineal surgery or trauma, Peyronie's, priapism, neurologic disease
- psychosocial hx } past & present partner relationships, job status, \$\$\$, family situation
- meds (old & new), allergies, EtOH, smoking, recreational drugs
- assess for contraindications to drug therapy

2) P/E

- general appearance (body habitus), vitals (BP)
- secondary sexual characteristics, gynecomastia
- abdo exam } masses, palpable bladder, CVA tenderness
- genital exam } phallus size, chordee, Peyronie's plaque, testis size, DRE, rectal tone
- cardiac exam
- **peripheral vascular exam**
- neuro exam } peripheral, spinal, supraspinal (somatic, autonomic)

3) lab tests

- **fasting glucose + HbA1C**
- **lipid profile**
- **am testosterone**
- PSA if life expectancy >10yrs

What are the advantages & disadvantages of the different treatment options for ED?

	ADVANTAGES	DISADVANTAGES
Counseling	<ul style="list-style-type: none">- noninvasive- resolves conflict	<ul style="list-style-type: none">- high recurrence rate of ED
Oral drugs (PDEIs)	<ul style="list-style-type: none">- noninvasive- 60-70% efficacy	<ul style="list-style-type: none">- systemic side effects- nitrate contraindication
vacuum device	<ul style="list-style-type: none">- minimally invasive	<ul style="list-style-type: none">- unnatural erection- absence of spontaneity- local side effects (petechiae, pain, cold penis)
transurethral drugs (MUSE)	<ul style="list-style-type: none">- minimally invasive	<ul style="list-style-type: none">- local side effects (pain, urethral bleeding, hypoTN)- low efficacy
ICI	<ul style="list-style-type: none">- 90% efficacy	<ul style="list-style-type: none">- more invasive- local side effects (priapism, fibrosis, pain)
prosthesis	<ul style="list-style-type: none">- high success rate	<ul style="list-style-type: none">- need surgery + GA- risk of infection, fibrosis
vascular sx	<ul style="list-style-type: none">- restores natural erection	<ul style="list-style-type: none">- need surgery + GA- low efficacy of venous surgery- arterial bypass only for select pts

EVALUATION OF THE COMPLEX PATIENT

What are the indications for specialized testing for ED? }} **PETER Penis Loves SPORT**

- 1) **Peyronie's**
- 2) **Early onset (primary ED)**
- 3) **Trauma to pelvis/perineum**
- 4) **Endocrinopathy (complex)**
- 5) **Relationship problems**
- 6) **Pre-op**
- 7) **Legally sensitive case**
- 8) **Sleep disorder suspected**
- 9) **Psychogenic cause suspected**
- 10) **Obscure cause of ED**
- 11) **Refractory to therapy**
- 12) **Trial setting (measurement of drug effects in placebo-controlled drug trial)**

What are the different types of specialized tests used for ED?

→ NO TESTS HAVE GRADE A RECOMMENDATION IN EVALUATION OF ED

→ those listed below all have grade B recommendation

- 1) **vascular**
 - aimed at Dx of arterial and veno-occlusive dysfunction
 - 1st line
 - **Combined ICI + Stimulation testing** } N CIS = N venous occlusion (CIS)
 - 2nd line
 - **ICI + color Doppler U/S** } **provides excellent vasculogenic information**
 - } also good for high-flow priapism and localization of a ruptured artery
 - 3rd line
 - dynamic infusion cavernosometry and cavernosography (DICC)
 - } invasive (need 2 needles in penis for NS infusion + pressure recording)
 - } must have complete smooth muscle relaxation (need multiple injections of vasoactive agent)
 - } flow rate req'd to maintain erection at >100 mmHg = <5ml/min
 - arteriography } assess internal iliac, internal pudendal, and penile arteries (grade C) } good for anatomic info but poor functional info
 - } also assess inferior epigastrics → most commonly used for penile revascularization sx
- 2) **neurophysiologic**
 - nocturnal penile tumescence } used mainly to r/o psychogenic ED & rigidity testing (NPTR)
 - results are relatively free from psychologic influences
 - 80% of NPT occurs during REM
 - } also assess for sleep disturbances
 - } NOT part of routine ED evaluation
 - bulbocavernosus reflex latency, dorsal nerve conduction tests, etc
- 3) **audiovisual sexual stimulation**
 - enhances penile responses to a variety of test stimuli (vibration, ICI, PDEIs, etc)

Vasculogenic ED

What are the normal parameters on color Doppler U/S of the penis?

- often performed after ICI (alprostadil 20-60µg) + stimulation
- N arterial PSV is >35 cm/sec → N arterial EDV is <5cm/sec
- N RI at 20min is ≤0.9 → N arterial dilation after ICI is >75% (N is >1.5mm)
- abN = peak systolic arterial flow <25cm/sec
 → pudendal artery lesion
- asymmetrical cavernous arterial flow >10cm/sec = significant atherosclerotic lesion
 → cavernous artery lesion
- PSV >25cm/sec + EDV >5cm/sec + early detumescence after ICI = veno-occlusive dysfxn
- Resistive index at 20 mins <0.75 = venous leakage

What are the main indications for arteriography in the evaluation of ED?

- mainly to get anatomic info to plan surgical reconstruction
- 1) young male with ED secondary to traumatic arterial disruption
- 2) hx of perineal compression injury

What are the main indications for DICC?

- young male that is candidate for penile vascular surgery with:
- 1) hx of pelvic trauma
- 2) hx of primary ED

What are some other historical or investigational tests for vasculogenic ED?

- penile brachial pressure index (PBI)
- infrared spectrophotometry
- MR angiography
- penile plethysmography
- radioisotopic penography
- cavernous smooth muscle content (Bx)

Psychogenic ED

What are the main indications for NPT testing? }}} Penis Loves SPORT

- 1) Pre-op
- 2) Legally sensitive case
- 3) Sleep disorder suspected
- 4) Psychogenic cause suspected
- 5) Obscure cause of ED
- 6) Refractory to therapy
- 7) Trial setting (measurement of drug effects in placebo-controlled drug trial)

What are the normal findings on NPT testing (RigiScan)?

- loop placed on base of penis and at coronal sulcus
- **rigidity >70%** (nonbuckling erection) } rigidity <40% = flaccid penis
- increased tumescence of circumference >**3cm at base and >2cm at tip**
- number and duration } >**4-5 erections per night** (80% occur during REM)
 } duration of erection >**30mins**

What is the definition of ED?

- inability to attain and/or maintain a penile erection sufficient for sexual performance

What is the definition of psychogenic ED?

- persistent inability to achieve and/or maintain erection satisfactory for sexual performance due predominantly or exclusively to psychological or interpersonal factors
- generalized vs situational
- lifelong (primary) vs acquired

Neurogenic ED

What are some specialized tests used to assess for neurogenic ED?

→ effects of neurological deficit on erections is a complicated phenomenon

→ with a few exceptions, neurologic testing will rarely change management

1) somatic

- biothesiometry } measure sensory perception thresholds to vibratory stimulation
- sacral evoked response-BCR latency } abN if >3 standard deviations above mean of 30-40 ms
- dorsal nerve conduction velocity } avg is ~25 m/sec
- genito-cerebral evoked potential

2) autonomic

- heart rate variability and sympathetic skin response
- penile thermal sensory testing
- corpus cavernosum EMG

Hormonal ED

How much testosterone is normally produced by men?

- **4-8 mg/day**
- pulsatile manner } peaks in early AM, nadirs in evening
- ~**2% is free** (unbound) \ free + albumin-bound T accounts
- **38% bound to albumin** + other serum proteins / for **bioavailable T**
- **60% bound to SHBG**

List factors that affect SHBG production in the liver

→ ↑'s SHBG levels (less bioavailable T)

- elevated estrogen
- high T4
- aging
- cirrhosis
- anti-convulsants
- HIV infection

→ ↓'s SHBG (more bioavailable T)

- exogenous androgens
- GH
- obesity

What is the normal range for serum testosterone?

- AM testosterone should be >350 ng/dL (US)
- AM total testosterone 9-37 nmol/L (CANADA)

What happens to testosterone in the body?

- converted into DHT by 5AR } skin, liver, prostate, etc
- metabolized to estradiol by aromatase } brain, fat, liver, testes

What tests are involved in the hormonal evaluation of a complex ED patient?

- total/free/bioavailable testosterone
- SHBG (add albumin if severe liver disease)
- LH
- FSH
- prolactin
- TSH/T4
- adrenal failure

	ADVANTAGES	DISADVANTAGES
1) oral	- easy to administer	- inactivated by “first-pass” effect through liver (need higher doses) - liver toxicity - risk of liver Ca
2) trans-buccal	- more physiologic rhythm	- inconvenient - gum-related S/E's (16%)
3) transdermal (best) → patch → gel	- more physiologic rhythm - no “first-pass” effect through liver - easy to use	- local skin symptoms - can be transferred to others
4) injectable im	- cheap	- not physiologic rhythm - highest CV risk profile
5) pellet sc	- dosing only q3-6months	- not physiologic rhythm

What are the effects of high dose T on the liver?

- can lead to toxicity
- hepatitis
- cholestatic jaundice
- hepatocarcinoma
- hepatomas
- hemorrhagic liver cysts

What is the benefit of DHT instead of testosterone?

- not aromatized to estradiol } acts as pure androgen
- good in hypogonadal men predisposed to gynecomastia
- good for boys with constitutionally delayed puberty

List potential adverse effects of androgen replacement therapy } } } “ABC PPPIGS”

- Acne
- Baldness (male pattern)
- Cholesterol changes } moderate ↑ in LDL-cholesterol + ↓ in HDL-cholesterol \
- Platelet aggregation increases (mildly) } ↑'s CV risk
- Polycythemia/increased RBC mass /
- Priapism
- Infertility } LH and FSH suppression
- Gynecomastia, breast tenderness } conversion to estrogen
- Sleep apnea (induces or worsens)
- huge debate regarding effects on PSA and risk for PCa

What are the absolute contraindications to androgen therapy?

- “CHEAP Breasted SLuts” (or CLUB HOP)
- CHF (class 3 or 4)
- HCT >55%
- Elevated PSA (unexplained)
- Abnormal DRE (unexplained)
- Prostate Ca
- Breast Ca
- Sleep apnea (untreated)
- LUTS (IPSS >19)

What is the recommended f/u for men on androgen replacement?

- prior to initiation of Rx
 - CBC, LFTs and lipid profile
 - DRE + PSA
- TRUS Bx if abN PSA or DRE
- f/u while on T supplementation
 - DRE + PSA q3months x 1yr, then q1yr
 - consider Bx if PSA increases by >0.5 ng/mL during first 6 months
 - periodic CBC, Total Testosterone, LFTs, cholesterol and lipid profiles
 - must watch for sleep apnea
- efficacy determined by clinical response rather than repeat T testing

What is the management of ED due to hyperprolactinemia?

- 1) stop offending drugs } estrogens, morphine, sedatives, neuroleptics, etc
 - 2) bromocriptine (dopamine agonist)
 - 3) surgical ablation } failed bromocriptine or visual changes
- may eventually need T supplementation as T levels don't always return to N despite normalization of prolactin

List clinical features of hyperprolactinemia

- oligomenorrhea/amenorrhea
- galactorrhea
- infertility
- sexual dysfunction } decreased libido, ED
- visual problems
- H/A
- decreased TSH

Table 22-5 -- Alternative Therapies and Commercially Available ED Supplements

Alternative/Supplement	Overall Evidence
Acupuncture	Psychogenic ED; needs a randomized trial.
Androstenedione/DHEA	Increases estradiol and testosterone levels in men with normal testosterone levels; lowers high-density lipoprotein by an average of 10%. May increase testosterone levels dramatically in hypogonadal men. May benefit men with nonorganic and other ED and suboptimal levels of these precursors.
Ginkgo biloba	May have a blood-thinning effect. Lacks benefit in a study with men with ED.
Korean red ginseng (Panax ginseng)	Three preliminary trials suggest a potential benefit for men with ED, but quality control is a serious issue and more randomized trials are needed.
L-Arginine	A precursor to nitric oxide. High doses may benefit men who secrete low levels of nitric oxide. May lower blood pressure. Needs more randomized trials.
Yohimbine	Supplements probably contain little to no yohimbine. Prescription form is best and may benefit some with psychogenic ED. Can cause serious side effects.
Zinc	May benefit those with a severe zinc deficiency. Otherwise, data are lacking and high dosages can be dangerous and immunosuppressive.
Other supplements	<i>Avena saliva</i> and other potential cholesterol and blood-pressure reducers and <i>Tribulus terrestris</i> (precursor to DHEA) need clinical trials. Recent study of a Chinese herbal combination demonstrated no impact on sexual function versus placebo.
Antioxidants in combination with orally approved FDA medications	Folic acid plus vitamin E may enhance the response to sildenafil in men who failed to respond initially. Other oral drugs plus other supplements (e.g., yohimbine and arginine) may enhance erection. Large placebo-controlled trials are needed.

Non-Specific Non-Surgical Rx

What are the different types of PDE-5 inhibitors (CHART)?

- 1) sildenafil (Viagra) → 25, 50, 100mg
 - onset of action 15-60 min with 40% bioavailability
 - $T_{1/2}$ = 3-5hrs
 - blue-hue vision } cross-reactivity with PDE-6
- 2) vardenafil (Levitra) → 5, 10, 20mg
 - onset of action 15-60 min with 15% bioavailability
 - $T_{1/2}$ = 4-5hrs
 - blue-hue vision possible but much less common } cross-reactivity with PDE-6
 - only PDE5I with cardiac conduction precaution (**QT prolongation**)
- 3) tadalafil (Cialis) → 20mg (now daily dose – 2.5mg, 5mg)
 - onset of action 15-120 min (bioavailability not tested)
 - $T_{1/2}$ = 17.5hrs
 - can have some food
 - lower back muscle pain } cross-reactivity with PDE-11

What are the common side effects of PDE-5 inhibitors?

- headache (most common)
- flushing
- slight lowering of BP
- dyspepsia
- rhinitis
- priapism
- nonarteritic anterior ischemic optic neuropathy (NAION) } rare (RFs - older age, HTN, ↑ lipids, etc)

Which patients have PDE-5 inhibitors been found to be effective?

- general population with ED
- DM
- post-RP } directly related to degree of nerve-sparing, younger age, and lower stage
- post-EBRT

What are the contraindications to PDE-5 inhibitor RX?

→ ABSOLUTE

- use of nitrates

→ RELATIVE

- severe CV disease
- LV outflow obstruction
- MI within last 90 days
- unstable angina or angina during sex
- NYHA class ≥ 2
- uncontrolled arrhythmias, hypoTN, or uncontrolled HTN
- stroke within last 6 months
- hereditary retinal disorder (eg retinitis pigmentosa)
- high risk of priapism (sickle cell anemia, leukemia, etc)

What are the 3 risk categories of CV disease in ED patients (Princeton criteria - CHART) ?

1) low-risk

- asymptomatic and < 3 CV risk factors
- controlled HTN
- mild, stable angina
- post-revascularization
- MI $> 6-8$ wks ago
- mild valvular disease
- NYHA class 1 CHF

→ Rx ED as needed

2) intermediate-risk

- asymptomatic and ≥ 3 CV risk factors
- moderate, stable angina
- MI < 6 wks ago but > 2 wks ago
- NYHA class 2 CHF
- noncardiac sequelae of atherosclerotic disease

→ cardiac w/u to reclassify as low- or high-risk

3) high-risk

- unstable or refractory angina
- uncontrolled HTN
- NYHA class 3/4 CHF
- MI within last 2 wks
- HOCM
- high-risk arrhythmia
- moderate to severe valvular disease (especially AS)

→ defer Rx until cardiac condition is stabilized

List major CV RFs (CHART)

- age
- Male gender
- HTN
- DM
- smoking
- \uparrow 'd cholesterol
- sedentary lifestyle
- Fm Hx of early CAD

What are the indications to dose reduce PDE5 inhibitor therapy?

1) use of α -blockers (except flomax)

2) liver failure

3) renal failure

4) ≥ 65 yrs old (start at 25mg)

5) meds that block CYP3A4 pathway

→ protease inhibitors (HIV)

→ ketoconazole, itraconazole

→ cimetidine

→ CCB (verapamil)

→ cyclosporine

→ cipro

*** if using α -blockers, no need to adjust w/ Cialis but need to wait 4hrs after Levitra & Viagra ***

What is the management of those on PDE-5 inhibitors that have angina/MI during sex?

- past use of nitrates >2wks ago is NOT a contraindication to PDE5I
- stop sexual activity and relax } go to ER if pain persists
- nitrates can't be used in treatment of MI
- avoid nitrates for 24hrs after sildenafil and vardenafil; 48hrs for tadalafil

What is the management of hypoTN after nitrates + PDE5Is?

- Trendelenburg + iv fluids
- α -agonists (phenylephrine) PRN
- IABP for refractory hypoTN

What is papaverine?

- alkaloid from opium poppy
- **PDE2,3,4,5 inhibitor** } **increases cGMP & cAMP**
- **also CCB effect**
- metabolized in liver
- $T_{1/2}$ = 1-2hrs
- priapism and fibrosis, can raise LFTs

What is phentolamine?

- **competitive α -blocker** } α_1 and α_2 affinity
- $T_{1/2}$ = 30 mins
- hypoTN, reflex tachycardia, nasal congestion, GI upset

What is alprostadil?

- **PGE1**
- smooth muscle relaxant, vasodilator, platelet aggregation inhibitor } **increased cAMP**
- metabolized by PG-15-hydroxydehydrogenase (present in penis)
- $T_{1/2}$ = 60 mins
- painful erections (almost never see priapism)

What are the advantages & disadvantages of the different ICI agents (CHART)?

	ADVANTAGES	DISADVANTAGES
Papaverine (20 – 60mg)	<ul style="list-style-type: none">- cheap- stable at room temp	<ul style="list-style-type: none">- fibrosis, priapism- can raise LFTs
Papaverine + Phentolamine (0.1 – 1.0 mL)	<ul style="list-style-type: none">- more effective	<ul style="list-style-type: none">- fibrosis, priapism
Alprostadil (2.5 - 60µg)	<ul style="list-style-type: none">- rarely see priapism	<ul style="list-style-type: none">- painful erections- ***, needs refrigeration
Papaverine + Phentolamine + Alprostadil (0.1 – 1.0 mL)	<ul style="list-style-type: none">- most potent- no painful erections	<ul style="list-style-type: none">- needs refrigeration
Moxisylyte (10 – 30mg)	<ul style="list-style-type: none">- rarely see priapism	<ul style="list-style-type: none">- less potent

What are the contraindications to ICI therapy for ED?

→ ABSOLUTE

- 1) sickle cell anemia
- 2) schizophrenia or severe psych disorder
- 3) severe systemic disease (unstable CAD)
- 4) penile prosthesis

→ RELATIVE

- 1) use of anticoagulant or ASA
 - compression x 5-10 min

List GU manifestations of sickle cell disease/trait. (AUA Update #18 – '05)

→ HUGE F'N PRIAPISM

- Hematuria (dysmorphic RBCs) } M > F and L side 4x more than R
- UTIs
- Glomerular disease (MPGN, immune complex GN, etc) } leads to proteinuria
- ED
- Frequency, polyuria, etc (Nephrogenic DI)
- Nocturnal enuresis
- Priapism
- RTA (distal)
- Infertility
- ARF
- Papillary necrosis
- Infarcts (renal medulla, testicular)
- Slow (chronic) renal failure
- Medullary RCC (trait)

What are the potential complications of ICI?

- priapism
- fibrosis
- hematoma
- local pain
- nodules and plaques
- urethral injury

What are the side effects of intraurethral MUSE?

- male urethral system for erections } 250 µg, 500 µg, 1000 µg
- alprostadil
- male } penile pain (dose-related)
 - } **hypoTN (can faint in office during trial)**
 - } syncope
 - } urethral bleeding
 - } headache
- partner } vaginal discomfort

What are some centrally acting drugs used for ED?

- 1) yohimbine } **α₂-blocker** from bark of yohim tree
 - } no difference than placebo in RCT (6mg po tid x 10 wks)
 - may have role in psychogenic ED
 - } mild side effects
 - **GI upset, headache, anxiety, slight increase in BP, palpitations**
- 2) trazodone } mild **antidepressant**
 - } can lead to priapism
 - } not beneficial over placebo for organic ED
- 3) apomorphine } unrelated to morphine
 - } **dopamine agonist (D₁ and D₂ activation)**
 - acts on paraventricular nucleus (PVN)
 - } rapid onset of action (10-20 mins)
 - } side effects include **nausea, yawning**, dizziness, sweating, drowsiness
- 4) melanocortin-receptor agonists } proerectile and increases sex drive
 - } side effects include **yawning & nausea**

PREMATURE EJACULATION

What is the definition of premature ejaculation?

→ evolving } DSM-4 1994 definition, WHO 1994 definition

→ **3 essential components to all definitions:**

- 1) short ejaculatory latency } <2 minutes**
- 2) lack of control**
- 3) sexual dissatisfaction**

What are the exclusionary criteria for a Dx of premature ejaculation?

- 1) associated with alcohol, substance use, or meds
- 2) in context that leads to very high levels of arousal (new partner, novel situation, etc)
- 3) low frequency of sexual activity

What is the average intravaginal ejaculatory latency time?

- 2-10 minutes

What is the classification of premature ejaculation?

- 1) lifelong vs acquired
- 2) situational/partner related vs global

What are the potential causes of premature ejaculation (CHART)?

→ biologic (SHHHEG)

- 1) serotonin receptor dysfunction
- 2) hypersensitivity (larger portion of cerebral cortex dedicated to dorsal nerve of penis)
- 3) hyperexcitable ejaculatory reflex
- 4) hyperarousability
- 5) endocrinopathy
- 6) genetic predisposition

→ psychogenic

- 1) anxiety
- 2) psychodynamic
- 3) evolutionary
- 4) early sexual experience
- 5) poor ejaculatory control techniques
- 6) infrequent sex

What is the recommended work-up for premature ejaculation?

- 1) history } medical hx, surgical hx, sexual hx (desire, arousal, and ejaculation), meds, drugs, alcohol use
 - } lifelong vs recent problem, global vs situational problem
 - } estimated intravaginal ejaculatory latency time, level of distress, frequency of sex
 - } partner's assessment of situation
- 2) physical exam } focus on signs of chronic disease
 - vascular disease
 - endocrine disease
 - neurological disease
 - } genital exam
 - Peyronie's
 - DRE

What are the management options for premature ejaculation? (includes AUA Update #37 - 2007)

- 1) psychological/behavioural therapy
 - } stop-squeeze method
 - } stop-pause method
 - 2) pharmacologic therapy
 - } SSRIs eg paroxetine, sertraline, fluoxetine
 - **Paxil 20-40mg OD has best efficacy in delaying ejaculation**
 - S/E } fatigue, yawning, mild nausea, loose BM, sweating
 - } topical anesthetic eg EMLA cream
 - local side effects in male and female
 - } TCA eg clomipramine
 - nonselective serotonin reuptake inhibitor
 - better than SSRIs for on-demand Rx (take 5hrs before)
 - } SNRIs eg tramadone
 - opioid with serotonin & NE reuptake inhibition
 - } PDE-I
 - if acquired premature ejaculation secondary to ED
- if any ED, must treat ED first**
- ejaculatory control more likely to be restored for acquired premature ejaculation compared to lifelong primary premature ejaculation**

List meds used for premature ejaculation. }} “Slower Cum with Premature Ejaculation Therapy”

- **SSRIs** } Paxil (1st line), Fluoxetine, Sertraline
- **Clomipramine**
- **PDE5-I**
- **EMLA cream**
- **Tramadol**

- inform pt of alternative options } vacuum device, ICI, etc
- discuss various types of penile prosthetic devices } malleable vs inflatable
- discuss expectations of surgery } glans doesn't enlarge, erections usually shorter than N
 } does not increase orgasm or ejaculation
- post-op management } pain meds for ~1wk, no sex for 4-6 wks,
- discuss complications } infection, mechanical failure, irreversible changes

SURGICAL APPROACHES

What are the different surgical approaches taken for penile prosthetic implantation?

- 1) subcoronal } only for malleable or positional devices
- 2) infrapubic
- 3) penoscrotal

List advantages & disadvantages of infrapubic & penoscrotal approaches to penile prosthesis insertion (CHART)?

	ADVANTAGES	DISADVANTAGES
Infrapubic approach	- reservoir placed under direct vision	- limited corporeal exposure - possible dorsal nerve injury - inability to anchor pump
Penoscrotal approach	- better corporeal exposure → especially if corporeal fibrosis significant - no dorsal nerve injury - pump fixation possible	- blind reservoir placement - potential excess tubing present in scrotum or base of penis

AMS 700 ULTREX INFLATABLE PROSTHESIS IMPLANTATION BY TRANSVERSE PENOSCROTAL APPROACH

List ways to reduce likelihood of infection of penile prosthesis

- avoid surgery in patients with UTI, skin infections in the operative field, etc
- shaving to be done just before surgery } use clipper not razor
- 10-min skin prep
- broad-spectrum Abx 1hr pre-op } eg Amp + Gent
- use of paper drapes not cloth drapes } less permeable to bacteria when wet
- use of Abx-coated device or submerge in Abx solution until insertion time
- good control of blood sugars

Describe the main points of an inflatable penile prosthesis implantation.

→ exposure

- patient in supine position under GA or spinal
- 4cm transverse incision made ~1cm below penoscrotal junction
- transverse incision carried down through dartos fascia } towards urethra & corporeal bodies
NOT towards scrotum
- underside of dartos fascia dissected off urethra and proximal crura
- ring retractor placed

→ placement of cylinders

- 2cm corporotomies made w/ placement of 2 horizontal mattress sutures on each side
- dilation starts with 8mm Hegar dilators } proceeds to 16mm proximally and 14mm distally
- sizing instrument used to measure distal and proximal ends
 - 2cm corporotomy not included in total length } eg 9cm + 11cm = 20cm device
 - there are standard sizes } adjustments made by addition of rear tip extenders
- cylinders filled with NS until full but not under pressure
- pump filled with NS
- reservoir filled with NS to remove air, then NS is removed
- distal cylinder inserted with aid of Furlow inserter
- rear tip extenders added PRN then proximal portion is inserted manually
 - proper placement = proximal end all the way to attachment of crus to pelvic bone
+ distal end under midglans + flatly lying cylinder w/in corporal bodies
- corporotomies closed by tying horizontal stay sutures } proximal sutures closed first

→ placement of pump

- 2nd incision made through dartos fascia in scrotal septum
- pump placed in deep septal pouch within scrotum
- each of the 3 pump tubes are routed through back wall of pouch
- pump tubes connected to each cylinder
- 2nd dartos incision closed

→ placement of reservoir

- pubis to glans tip measured with cylinders in flaccid and inflated positions
- bladder emptied by placement of Foley
- reservoir placed into retropubic space through primary penoscrotal incision
- transversalis fascia perforated in floor of external inguinal ring just above pubic tubercle on either side
 - correct placement confirmed by feeling back of pubis and balloon in bladder
- empty reservoir introduced in retropubic space
 - 65cc reservoir for all devices except for 18cm & 21cm cylinders (100cc reservoir)
- reservoir filled and should confirm pressure in reservoir is zero even with S/P pressure
 - back pressure test to prevent autoinflation
- 3rd pump tube connection made between reservoir and pump
- placement of JP drain
- dartos fascia closed transversely
- skin closed with subcuticular 4-0 vicryl

POST-OP CARE

What is involved in the post-op care after implantation of a penile prosthesis?

- remove Foley and JP drain next morning
- keep penis up against lower abdomen
- continue po Keflex x 1wk
- oral pain meds
- no heavy lifting for 4-6 wks if reservoir placed } don't want displacement into inguinal area
- cylinder cycling can begin in 4-6 wks } inflate and deflat BID for 1 month
- can have sex once inflation can be accomplished without pain
 - can initially get failure to reach orgasm

COMPLICATIONS

What are the potential complications following penile prosthesis implantation?

1) perforation } can occur during dilation of proximal corpora (crura)

→ **usually occurs proximally & medially near attachment to pelvic bone**

} can also occur during dilation of distal corpora

→ can cross over to other side or even perforate the urethra

Rx → proximal/crura perforation

- use larger dilator to dilate correct track
- insert cylinder into correct track & allow perforation to heal
- rarely will need “wind sock correction”

→ distal perforation

- perforation into urethra = stop and place Foley x 7-10days
- perforation on “virgin” 1st side = stop and reschedule
- perforation on 1st side with hx of previous perf/scarring = stop
+ repair perforation + S/P vesicostomy or PU
- perforation on 2nd side = stop and leave only 1 OR can place both

2) erosion } occurs post-operatively

} can have erosion out through cavernosum or into urethra (more common for malleable prostheses and in men with SCI)

Rx → through lateral cavernosum

- fold back cylinder and make incision in back wall of capsule, proximal to erosion site
- dilation of true corpus cavernosum followed by insertion of distal cylinder with Furlow inserter

→ through urethra

- if malleable, only eroded side removed + Foley x 10 days
- if inflatable, remove eroded cylinder ASAP + plug tubing
- second rod may not be necessary for sex

3) infection } most significant complication b/c removal of all components is usually req'd

→ 1-3% for 1st time prostheses

→ 5-20% after revision surgery (if only failed component removed)

} **early (1-3wks) → usually gram -ve**

→ usually swelling, erythema, tenderness, pus, fever

} **late (6-24months) → usually gram +ve (*S. epidermidis* is most common)**

→ more common after malfunction/leak

→ usually just persistent or recurrent long-term pain with skin adherent to pump

} erosion of a component means entire device is infected

} may be slightly more common in DM, SCI, and with infrapubic approach

Rx → can give trial of Abx but usually need removal of entire device

→ corporeal smooth muscle fibrosis makes reimplantation of cylinder difficult

→ expedient device reimplantation now recommended (2-3 months)

→ “salvage” procedure also an option (remove, irrigate, reinsert new, Abx)

4) SST deformity } poor glans support (“concorde nose” appearance)

} from inadequate distal dilation, too short cylinders, or anatomic variations

Rx → remove, perforate capsule distally, redilate, resize, insert longer cylinders (or same cylinders longer rear tips)

→ dorsal plication of glans back onto shaft of penis (for minor SST)

- 5) oversized cylinder or rod } usually complain of pain that doesn't subside or presents with erosion into meatus or through glans
} may get sigmoid (S) deformities
Rx → revision with reimplantation of smaller rods
- 6) pump migration } may migrate toward base of penis making use of pump difficult and also interfere with intromission
Rx → revision may be necessary
- 7) auto-inflation } partial inflation with physical activity
Rx → reduce risk by placing reservoir in retropubic /prevesical space and perform back pressure test
→ keep cylinders deflated during initial healing
- 8) mechanical failure } fluid leakage in inflatable devices
} **connector sites (most common)**
} cylinders (2nd most common)
} reservoir and pump (uncommon)
Rx → revision (5-10% by 5-10yrs)

List the potential complications of a penile prosthesis insertion.

→ “Old MAIMED Penis”

- Over-sized cylinder/rod
- Mechanical failure
- Auto-inflation
- Infection
- Migration of pump
- Erosion
- Deformity (SST)
- Perforation

What are the components of Dabs ABx solution?

→ in 100c NS

- 1) 500mg neomycin
- 2) 80mg gentamicin
- 3) 100mg polymyxin

What are the contraindications for immediate salvage of infected penile prosthetics?

- 1) necrotic infections
- 2) rapidly developing infections
- 3) erosion of cylinders
- 4) visible pus
- 5) clinically unwell
- 6) severe DM
- 7) immunocompromised

PENILE PROSTHESIS IMPLANTATION IN SPECIAL CASES

What are the ways to address penile curvature during prosthesis implantation for ED with concomitant Peyronie's disease?

- 1) prosthesis insertion itself may produce adequate straightening
- 2) modeling or forcefully bending penis with cylinders inflated
- 3) corporoplasty
 - multiple relaxing incisions } if gap defect is >1cm, should cover to prevent herniation of cylinder (PTFE, porcine SIS, cadaveric pericardium, etc)

Which conditions are associated with cavernosal fibrosis?

- makes dilation of corpora very difficult
- 1) post-removal of infected penile prosthesis
- 2) ED from ischemic priapism
- Rx → dilation with Metz not Hegar dilators
 - extended corporotomies } permits more controlled dilation +/- resection of fibrotic contents of corpus cavernosum

RESULTS

How successful are inflatable penile prostheses?

- durability } 80-90% at 5yrs without mechanical failure
- patient satisfaction } ~80% satisfaction
- partner satisfaction } ~70% satisfaction
- compared to other Rx } better erectile function and increased sexual activity compared to PDE5 inhibitors and ICI Rx

Chapter #24 – Vascular Surgery for ED

HISTORY AND REVIEW OF VASCULAR ED SURGERY

What are the goals of vascular ED surgery?

- arterial } goal is to bypass obstructive arterial lesions in internal iliac-cavernosal arterial bed to increase cavernosal arterial perfusion in a pt with pure arterial insufficiency
} **must have no end-organ disease**
- venous } goal is to decrease venous runoff in patients with pure venogenic ED
} must have no end-organ disease

COUNSELING OF THE PATIENT FOR VASCULAR ED SURGERY

What are the different incision sites for vascular ED surgery?

- semicircular incision on one side at base of penis } access to penile shaft & infrapubic region
- paramedian or transverse abdominal incision } exposure to inferior epigastric vessels
- midline abdominal incision } access to bilateral inferior epigastric vessels and penile shaft

PENILE ARTERIAL RECONSTRUCTION (PENILE REVASCULARIZATION)

List the features of an ideal candidate for microvascular arterial bypass surgery (CHART)?

- young & psychologically stable
- no vascular RFs } DM, HTN, CAD, smoker
- hx of blunt perineal or pelvic trauma } obvious recollection or probable occurrence of event
- has considered conservative Rx } responds to low-dose injections w/ a sustained, relatively rigid erection
- highly motivated for natural, spontaneous, rigid sustained erections without “assistance”
- failure to fill ED pattern
- reduced erectile spontaneity and rigidity
- variable sustaining capability (normal or better in AM)
- normal libido, ejaculation, orgasm and penile sensation
- normal penile geometry (flaccid and erect penile diameter-to-length ratio)
- normal penile extensibility during stretching
- no Peyronie’s plaques, intracavernosal masses, or nodules
- no sensory neuropathy
- should have demonstrated functional arterial disease, based on 2nd phase DICC & doppler U/S
 - gradient >30 mmHg between penile occlusion pressure and mean brachial pressure
 - PSV <25 cm/sec in corporal penile arteries

What imaging tests are used prior to vascular ED surgery?

- 1) common iliac arteriogram
 - 2) selective internal pudendal arteriogram
- identify focal lesion in artery/arteries supplying corpora cavernosa
- assess adequacy of proposed donor artery (eg inferior epigastric artery) and proposed recipient artery (eg branch of dorsal penile artery)

What are the potential donor arteries used for vascular ED surgery (CHART)?

→ microvascular surgery (endothelium preservation)

→ inflow

1) **inferior epigastric artery**

2) reversed saphenous vein connected to superficial femoral artery

→ outflow

1) **to dorsal penile artery (or branch)**

→ modified Michal

→ end-to-side or end-to-end

→ can preserve fundiform & suspensory ligaments

2) to isolated segment of deep dorsal vein that has good communicators to intracavernosal tissue

→ modified Virag

→ end-to-end

→ usually need to cut fundiform & suspensory ligaments (risk of penile shortening)

3) dorsal vein-penile artery fistula (Hauri)

Describe the main points of penile revascularization surgery for ED?

- pre-op Ancef

- supine with legs slightly abducted

- shave abdomen and genitalia prior to prep and drape

- sterile Foley placement

- have hand-held Doppler, papaverine, and phenylephrine available

- 2 common incisions

→ midline incision (umbilicus to base of penis)

- exposure for both inferior epigastrics & exposure to penile shaft

→ semicircular incision at one side of base + paramedian abdominal incision on other side

- proximal and distal exposure of penile NVB, preservation of fundiform & suspensory ligaments, no scars on penis

- skin and dartos layer stripped away from penile shaft

- identify and expose L and R dorsal penile arteries and the deep dorsal vein in between

→ dorsal nerves are lateral to dorsal penile arteries

- isolate and harvest inferior epigastric artery on undersurface of rectus muscle

→ take with surrounding veins and fat en bloc to preserve vasa vasorum

→ dissect to origin at level of external iliac artery

- pass inferior epigastric artery through inguinal canal to the base of the penis

→ inspect origin of inferior epigastric for kinking or twisting

- abdominal incision closed (fascia + skin)

- 3 common anastomoses with 10-0 suture

→ dorsal penile artery

→ deep dorsal vein

→ dorsal vein-penile artery fistula

\
} end-to-end preferred for better inflow
/

- check flow with Doppler

- +/- placement of drain

- closure of inguino-scrotal incision (dartos + skin)

What is the blood supply to the penis?

- penile skin } **external pudendal** branch off femoral vessels

- penis } int. iliac → int. pudendal → common penile

1) **dorsal** → cavernous branches to corpora and also circumflex branches to spongiosum and urethra, ending in glans

2) **cavernosal** → straight and helicine arteries to cavernosum

3) **bulbourethral** → spongiosum, urethra, & glans

} accessory pudendal artery may also contribute

} other possible accessory arteries → from ext. iliac, obturator, vesical and femoral

What is the venous drainage of the penis?

→ all 3 systems can communicate

- 1) superficial (skin)
 - **superficial dorsal vein** → usually drains to **L saphenous vein**
- 2) **intermediate**
 - subtunical capillary plexus → emissary → circumflex → **deep dorsal veins** (w/in Bucks)
+ periurethral veins → **Santorini's plexus** → vesical plexus → internal iliac veins
- 3) deep
 - **crural, cavernosal, bulbar veins** → **internal pudendal veins** → internal iliac veins

What are the potential complications following penile revascularization surgery for ED?

- penile edema } common
- hematoma
- penile numbness (hypoesthesia)
- penile shortening (20%) } scar entrapment - more common if fundiform/suspensory ligaments cut
 - } may need scar release surgery
- mechanical disruption of anastomosis + hemorrhage
- glans hyperemia } from deep dorsal vein arterialization
 - } occurs if communicating vein from deep dorsal vein to glans in distal dissection is missed

What are the success rates of penile revascularization surgery for ED?

- 30-90% success
- failure often related to presence of "end-organ" disease or poor outflow/run-off

PENILE VENOUS SURGERY

What are the required parameters prior to penile VENOUS surgery for ED (CHART)?

- complaint of short-duration erections or tumescence only with sexual stimulation
- failure of PDE5I's or ICI
- normal cavernous arteries on 2nd phase of DICC or Doppler U/S
- faulty veno-occlusive mechanism determined by infusion pump or gravity pharmacocavernosometry that is amenable to surgery (no massive leakage)
- location of site of venous leak from corpora cavernosa on pharmacocavernosography
- no medical contraindication to Sx
- complete elimination of smoking
- selection on presentation of alternative choices in presence of long-term success rate of 40-50%
- goal is a thorough complete penile vein dissection and ligation

Describe the main points of penile venous surgery for ED?

- supine or dorsal lithotomy position
- sterile Foley placement
- semicircular peripenile incision
- entire penis inverted into wound
- **communicating veins between deep and superficial systems are ligated**
- indigo carmine injected into corpora cavernosa } helps demarcate draining cavernosal veins
- release of fundiform and suspensory ligament in infrapubic region
- **ligation of deep dorsal vein in midpenile shaft**
- direct communicators and communicators from circumflex veins ligated
- cavernosometry
 - to produce an erection
 - to demonstrate adequate veno-occlusion has been obtained
- reapproximate suspensory ligaments
- drain placed in infrapubic region & close skin

What are the potential complications following penile venous surgery for ED?

→ immediate

- penile and scrotal bruising
- penile edema
- pain from nocturnal erections
- wound infection
- hematoma

→ long-term

- penile shortening } 20-30%
- penile numbness (hypoesthesia)
- penile tethering from wound scar contraction

What are the success rates of penile venous surgery for ED?

- long term results (<1yr) show success of ~25%

Chapter #25 – Peyronie’s Disease

ANATOMIC CONSIDERATIONS AND ETIOLOGIC FACTORS

Name some diseases associated with Peyronie’s disease. } } } “Damn Painful Twisted Penis”

- 1) Dupuytren’s contracture (AD inheritance) } 30-40%
 - 2) Plantar fascial contracture (Ledderhose’s disease)
 - 3) Tympanosclerosis
 - 4) Paget’s disease
- DEBATABLE } DM, gout, trauma, β -blockers, PDE5I’s, ICI

What is the epidemiology of Peyronie’s disease?

- symptomatic incidence = 1-5%
- average age at onset = 53yrs
- more common among couples that engage in more vigorous sex
- 1/3 present with concomitant ED

What are the 2 layers of the tunica albuginea covering the corpora cavernosa?

→ composed of fibrillar collagen (mostly type 1 and some type 3) + elastin

- 1) inner circular layer } support
 - } intracavernous pillars radiate from inner layer for support
 - } emissary veins run between the inner and outer layer
 - 2) outer longitudinal layer } extends from glans to proximal crura, inserting into inferior rami
 - } absent between 5 and 7 o’clock (ventral groove) → weakest area
 - } compresses emissary veins during erection
 - } strength layer
- corpus spongiosum lacks intracorporeal struts and outer layer

What is the cause of Peyronie’s disease?

- buckling trauma that causes injury to septal insertion of tunica albuginea
- likely during sex } separation of outer longitudinal layer from inner circular layer
 - intravasation of blood with activation of fibrinogen to fibrin
 - influx of macrophages, neutrophils, and mast cells
 - thrombus forms leading to deposition of fibronectin + binding of growth factors
 - **TGF- β 1 is main growth factor involved in fibrosis & plaque formation**
 - matrix metalloproteinases may also be involved in abN scarring process
 - **failure to down-regulate MMPs can lead to plaque formation**

What are the histologic findings of Peyronie’s plaques?

- non-polarized arrangement of collagen
- haphazard arrangement of elastin
- entrapped fibrin

PATHOPHYSIOLOGY AND NATURAL HISTORY

What are the 2 phases of Peyronie's disease?

- 1) active phase
 - often associated with painful erections } 33% have painless deformity
 - deformity still changing
- 2) secondary quiescent phase
 - disappearance of painful erections if present
 - stabilization of deformity

What is the natural history of Peyronie's disease?

- rare to see "spontaneous resolution" } likely trauma that resolved w/o development of Peyronie's
- pain disappears in majority by ~1yr after presentation
- dorsal lesions are the most common
- most still able to have sex
- most do not need surgery
- if surgery is performed, ventral curvatures are associated with higher rate of post-op ED

SYMPTOMS

List 5 features of Peyronie's disease?

- penile pain with erection
- penile deformity, both flaccid and erect } can complain of tip flaccidity
- shortening with and without erection
- plaque (or indurated areas) in penis } most commonly on dorsal surface
- ED common } venogenic ED

EVALUATION OF THE PATIENT

What is involved in the evaluation of Peyronie's disease?

- 1) Hx } characterize lesions → mode of onset (sudden vs gradual), time of onset, affect on intercourse
 - } surgical hx (penile sx, instrumentation, etc)
 - } PMHx (Dupuytren's, plantar fasciitis, Paget's, etc),
 - } meds, allergies, drugs,
 - } psychosocial hx & sexual hx (ED and RFs for ED, ejaculation problems, partner, etc)
- 2) P/E } photographs of erection
 - } examine penis on stretch
 - } examine hands, feet, ears → r/o tympanosclerosis, Dupuytren's contractures
- 3) investigations } plain x-ray or U/S to identify calcifications (found in 30%)
 - } +/- vascular testing (colour Doppler U/S, DICC, etc) → if considering Sx

What are the non-surgical management options for Peyronie's disease?

[illegible]

- 6) CCB } inhibits formation of scar (collagen, fibronectin, GAG)
 - } verapamil 1mg/mL injection q2-4wks x 12 injections
 - } **decreased plaque size, improved curvature, improved tip flaccidity**
- 7) Interferon } inhibits scar formation (collagen, fibronectin, GAG)
 - } **improved curvature and improved ability to have sex**
- 8) Collagenase } enzyme involved in scar remodeling
 - } **still investigation but demonstrates improved curvature**
- 9) steroids } NOT RECOMMENDED due to significant local side effects + inconsistent results + risk of deterioration

→ TOPICAL therapy

- 10) steroids, verapamil, orgotein, etc } no efficacy in blinded studies

→ OTHER

- 11) RADs } NOT RECOMMENDED due to risk of malignant change and ED
- 12) ESWL } limited data
 - } favorable results in one case-controlled trial
- 13) Vacuum erection device } limited data

→ ensure stable (>6 months) & mature disease (asymptomatic) } usually wait at least 12-18 months from onset of disease

- 1) curvature that precludes intercourse
- 2) concomitant ED that precludes intercourse

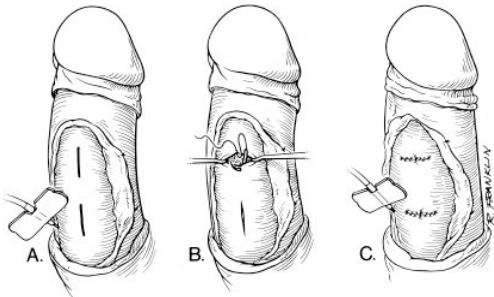
What are the surgical management options for Peyronie's disease?

→ shortening procedures

- 1) contralateral plication +/- excision of tunica albuginea
→ eg Nesbitt
- 2) corporoplasty
→ eg Yachia (Heineke-Mikulitz)
→ especially for men with ED
→ also good for ventral curvature (higher risk of veno-occlusive dysfunction)

→ non-shortening procedures

- 3) excision of plaque + grafting
→ SIS, vein graft, dermal graft, tunical vaginalis, temporalis fascia
→ less initial contraction seen with SIS and vein grafts
→ may not be ideal for men with ED
- 4) incisions through plaque + patching
→ dermis, porcine intestinal submucosa
- 5) penile prosthesis +/- remodeling of penile curvature
→ inflatable preferred
→ better results with device that has true controlled expansion cylinders
→ Abx-coated devices better



→ Yachia corporoplasty

Which skin incision is best for surgical repair of Peyronie's disease?

→ depends on location of lesion or location of proposed intervention

- 1) ventral plaques or ventral plications } ventral midline incision
- 2) dorsal plaques or dorsal plications } circumcising incision

What are the indications to proceed directly to penile remodeling + prosthetic implantation?

- 1) severe veno-occlusive disease
- 2) concomitant ED refractory to medical Rx

What are the potential complications of surgical management for Peyronie's disease?

→ early

- penile edema
- bleeding/hematoma
- infection
- urethral injury

→ late

- ED
- penile shortening
- insensate penis/numbness
- urethral stricture
- urethrocutaneous fistula
- suture granuloma
- graft loss
- penile skin loss
- recurrence
- hourglass deformation
- incomplete correction or overcorrection

Describe the important steps of excision + dermal graft procedure for Peyronie's disease.

- incision } dependent on location of lesion
 - ventral plaques } midline incision of ventral aspect of penis
 - dorsal plaques } circumferential incision
 - previous circ } use old circ scar
- deglove penis to its base
 - proximal plaques } 2nd incision on scrotum, lateral to base of penis
 - } lay skin aside, cover w/ warm sponge
- elevate dorsal NVB w/ Buck's fascia
 - incise just lateral to spongiosum, w/ Buck's and dorsal NVB dissected off lateral and dorsal corpora cavernosa
 - alternative } dissect sharply through bed of deep dorsal vein, perform modified vein dissection
- artificial erection to define curvature
- place Prolene stay sutures in midline, proximal, and distal to plaque
- mark incision
 - if excision of plaque planned, incise tunica laterally to convert corporotomy defect from ovoid to stellate
 - releases tightness of defects edges
- excise plaque
 - measure defect } stretch penis to ensure adequate coverage
- graft harvest
 - dermal graft outlined on donor site
 - graft site de-epithelialized, defat dermal graft
 - tailor graft to measure 30% larger in all dimensions
- grafting
 - complete closure w/ 3-0 PDS, perform another artificial erection, oversew leaks
 - close penis, reappose Buck's w/ PDS
 - small suction drains
- alternative } H incision
 - flaps allowed to slide, leaving approximately square defect
 - graft sutured onto defect
- penis covered w/ Bioclusive dressing, mildly compressive Kling (x4h)
 - check glans q30min x 4h
- Post-op
 - Foley x 1d
 - remove drains
 - initially suppress erections w/ Valium and amyl nitrate
 - after 2 weeks, encourage pts to have erections, but not sex
 - manipulate penis to prevent adherence of tissue
 - use vacuum device

NATURAL HISTORY

What is the natural history of priapism?

- either permanent resolution or progression to recurrent episodes +/- some degree of ED
- after resolution of episode of ischemic priapism, can have some penile edema and some enlargement may persist
- without effective treatment, even major episodes of ischemic priapism will eventually resolve with time, although permanent damage of the penis can be expected
 - ~90% of those with priapism >24hrs will have permanent ED
 - sexual ability better preserved if later age of onset of priapism
- non-ischemic priapism may persist unresolved for extended periods of time if not treated
- erectile function usually preserved in non-ischemic priapism
- sicklers and idiopathic priapism represent most with recurrent priapism

PATHOLOGY

What are the histopathologic features of ischemic priapism?

- penile tissue necrosis & progressive fibrosis are the end-stage manifestations
- smooth muscle contractile dysfunction results
- hypoxia, acidosis, glucopenia, hypercapnia, increased metabolic acid products at 4hrs
- trabecular interstitial edema after 12 hrs
- sinusoidal endothelial denudation with adherence of thrombocytes to exposed BM after 24 hrs
- formation of thrombi in sinusoidal spaces with necrosis of smooth muscle cells after 48 hrs
- reperfusion injury also occurs after resolution due to oxidative stress
- NO thrombi form despite intracorporal blood stasis due to increased fibrinolytic activity in the penis relative to systemic circulation
- irreversible damage starts at ~4hrs

PATHOPHYSIOLOGY

What is the pathophysiology of priapism?

- ischemic
 - veno-occlusion } vascular stasis with decreased venous outflow due to mechanical factors (eg sickle cell), local viscosity changes (eg IHD), and increased local coagulability (eg TPN)
- non-ischemic
 - unregulated blood inflow } traumatic disruption of penile vasculature with fistula formation b/w cavernous artery and lacunar spaces of cavernous tissue
- dysregulatory hypothesis } dysfunctional determinants of corporal smooth muscle responses

CLASSIFICATION

How is priapism classified?

- 1) ischemic priapism } low-flow priapism
 - features little or absent intracorporal blood flow } compartment syndrome of penis
 - get characteristic metabolic changes & excessive pressure increases localized to corpora cavernosa
 - typically presents WITH PAIN, rigid corpora cavernosa
 - glans & corpus spongiosum are usually not engorged
 - ABG of cavernous bodies show hypoxia, hypercapnia, and acidosis
- 2) non-ischemic priapism } high-flow priapism
 - features elevated vascular flow through the corpora cavernosa
 - most frequently associated with penile or perineal trauma
 - typically presents WITHOUT PAIN and corpora cavernosa are not usually fully rigid
 - ABG of cavernous bodies does not reveal hypoxia or acidosis
- 3) recurrent "stuttering" priapism
 - variant of ischemic priapism
 - most commonly seen with sickle cell disease
- 4) refractory priapism
 - non-ischemic erectile state that occurs immediately after treatment of ischemic priapism
 - due to rapid arterial blood filling after surgical treatment
- 5) neurogenic priapism
 - neurologic disorders causing disturbances in neuroregulation of penile erection at central or peripheral nervous system levels
 - fits both ischemic & non-ischemic priapism
- 6) idiopathic priapism
 - tends to be ischemic
- 7) drug-induced priapism
 - fits both ischemic & non-ischemic priapism

DIAGNOSIS

What is involved in the w/u of priapism?

- 1) hx and P/E } pain, duration, previous episodes, previous treatment, PMHx, meds, ICI
 } penis, DRE, abdo exam, neuro exam
- 2) Lab tests } CBC, sickle cell screen, serum & urine toxicology, penile ABG
- 3) imaging } should not delay treatment
 } color duplex U/S, penile arteriography
 → penile arteriography only used as part of embolization, NOT DIAGNOSTIC

What are the ABG findings of priapism?

- ischemic } PO₂ <30 mmHg, PCO₂ >60 mmHg, pH <7.25
 - non-ischemic } PO₂ >90 mmHg, PCO₂ <40 mmHg, pH ~7.4
- normal flaccid penis ABG is equal to normal mixed venous blood at room air
- PO₂ ~40 mmHg, PCO₂ ~50mmHg, pH ~7.35

What are the findings on color duplex U/S of priapism?

- must be done in lithotomy or frog-leg position } scan perineum and then entire penile shaft
- ischemic } minimal or absent blood flow in cavernosal arteries and within corpora cavernosa
 - non-ischemic } normal to high blood flow in cavernosal arteries and evidence of blood flow in corpora cavernosa
- } may also see cavernous arterial fistula or pseudoaneurysm that helps confirm the diagnosis of non-ischemic priapism

TREATMENT

What is the treatment algorithm for priapism?

- 1) Hx, P/E, ABG
 - ischemic vs non-ischemic
 - isolated vs stuttering
- 2) if stuttering
 - anti-androgens, self-injection with phenylephrine, baclofen, digoxin, etc
- 3) if ischemic
 - a) aspiration +/- irrigation } simultaneous treatment of underlying cause (eg sickle cell)
 - b) phenylephrine
 - c) distal shunting
 - d) proximal shunting
 - e) penile prosthesis
- 4) if non-ischemic
 - a) observation
 - b) arteriography and embolization
 - c) surgical ligation

Ischemic Priapism

What are the non-surgical management options for ischemic priapism? (AUA Guidelines 2003)

- IF AN UNDERLYING ETIOLOGIC DISORDER EXISTS, CONCURRENT SYSTEMIC TREATMENT SHOULD BE PROVIDED BUT DON'T DELAY SPECIFIC MGT
 - eg. Hydration, oxygenation, analgesia, exchange transfusion for sickle cell disease
- 1) aspiration +/- irrigation
 - place dorsal nerve block or local penile shaft block
 - use 16- or 18-gauge needle
 - transglanular intracorporal needle insertion may be best
 - lessens formation of penile hematoma
 - may facilitate drainage of blood into corpus spongiosum
 - maximal irrigation of corporal bodies done with patient in lithotomy and placement of needles into corpora cavernosa distally and proximally at penile crura
 - RESOLVES PRIAPISM IN ~30%
- 2) intracavernous injection of α -adrenergic sympathomimetics agents
 - evacuate stagnant blood prior to injection
 - phenylephrine is preferred α -selective adrenergic agonist
 - minimal risk of cardiovascular side effects
 - 100-500 μ g q5-10 mins until detumescence (MAX 1000 μ g)
 - monitor for S/E's such as HTN, tachycardia, H/A, reflex bradycardia, palpitations, arrhythmias
 - **BP and ECG monitoring recommended in patients w/ high CV risk**
 - RESOLVES PRIAPISM IN ~60%
 - UNLIKELY TO RESOLVE IF PRIAPISM DURATION >48-72 HRS

What are the potential side effects from intracorporal α -agonist injection?

- from entry into systemic circulation
- acute HTN
- H/A
- reflex bradycardia
- tachycardia
- palpitations
- cardiac arrhythmias

What are the different DISTAL SHUNTS used for ischemic priapism?

→ corporoglanular shunts

- 1) Winter } Bx needle into glans through tunica albuginea into corpus spongiosum
- 2) Ebbehøj } scalpel blade
- 3) El-Ghorab } transglanular incision with excision of tips of corpus cavernosum
 } creates shunt between corpora cavernosa and glans
 } most effective distal shunt

What are the different PROXIMAL SHUNTS used for ischemic priapism?

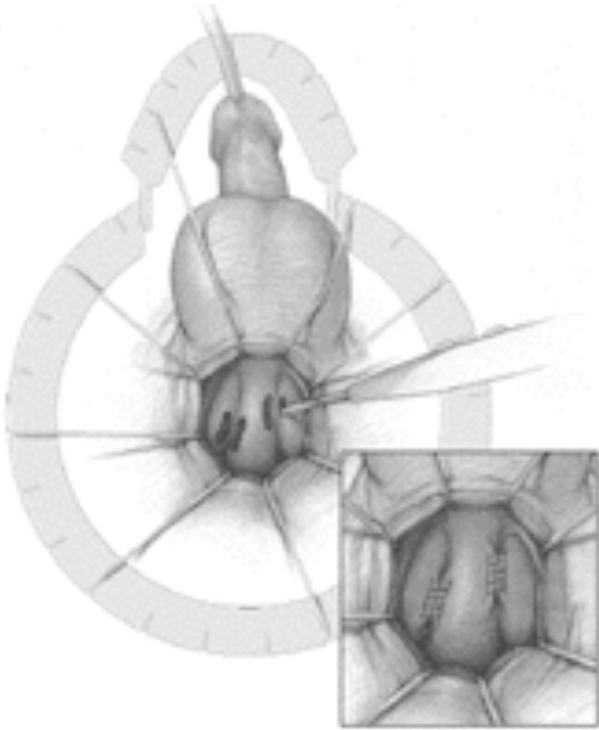
- 1) Quackel } creation of window between **corpus cavernosum & corpus spongiosum**
 } corporospongiosal shunt
 } placed between urethral bulb and crura via perineal approach
 → avoid penile approach due to risk of urethral injury
 } Sacher = bilateral Quackel
 - 2) Grayhack } anastomosis of **saphenous vein** to one of the corpora cavernosa
 } incision made 3-4cm below inguinal ligament and vein mobilized for 10cm
 } dissect subcutaneously to corpora and pass ligated vein
 } high risk of PE
 - 3) Barry } caverno-dorsal shunt
 } **superficial & deep dorsal veins** to corpora cavernosum
- most shunts tend to close in time
→ persistence of a shunt may be a cause of ED } length of priapism may contribute to ED

What are the potential complications of surgical shunts?

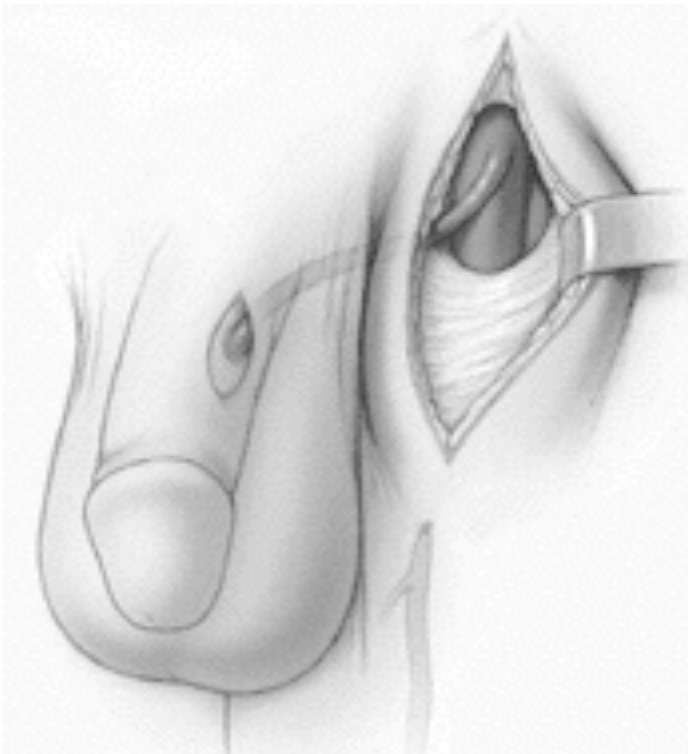
- hematoma
- pain
- scarring
- urethral fistulas
- purulent cavernositis
- PE (reported after Grayhack)

What is the role of immediate placement of a penile prosthesis?

- ischemic priapism presenting in a significantly delayed fashion will likely fail even proximal shunting and ED is likely inevitable
- immediate placement of prosthesis is advocated for several reasons;
 - 1) later Sx after fibrosis has evolved is very difficult and has higher complication rate
 - 2) these patients commonly do not respond to even ICI



→ PROXIMAL SHUNT } QUACKEL (unilateral) and SACHER SHUNT (bilateral)



→ PROXIMAL SHUNT } GRAYHACK SHUNT

Non-ischemic Priapism

List the management options for NON-ISCHEMIC priapism.

- 1) Observation
 - **recommended initial management**
 - spontaneous resolution occurs in ~60% of cases
- 2) selective arterial embolization
 - nonpermanent } autologous clot, absorbable gels
 - permanent } coils, ethanol, polyvinyl alcohol particles, acrylic glue
 - similar success rates
 - resolves non-ischemic priapism in ~75%
 - non-permanent preferred due to lower ED rate (5% vs 40%)
- 3) penile exploration and direct surgical ligation
 - ligation of sinusoidal fistulas or pseudoaneurysms using intra-op color duplex U/S
 - resolves non-ischemic priapism in ~65%
 - causes ED in up to 50%

Recurrent “stuttering” Priapism

What are the preventative strategies used for stuttering priapism?

- treat acute presentations as ischemic priapism
- **“Viagra TAMED HIS Boner”**
- 1) **Viagra** 25mg od
- 2) Terbutaline (β -agonist)
- 3) Anti-androgens
 - **primary recommendation } should not be used in prepubescent boys**
 - **most consistently successful**
 - Leuprolide (7.5mg im qmonthly) } hot flashes, gynecomastia, decreased libido
 - bicalutamide (50mg od) } hot flashes, gynecomastia, decreased libido, diarrhea
 - flutamide (250mg tid) } hot flashes, gynecomastia, decreased libido, edema, rash
 - 5 ARIs
- 4) **Methylene blue**
 - for non-ischemic priapism
- 5) **Estrogen**
- 6) **Digoxin** (0.5mg od)
 - cardiac glycoside } anorexia, N/V, blurred vision, H/A, gynecomastia
- 7) **Hydroxyurea**
 - in sickle cell patients
- 8) **Intracavernous self injections of phenylephrine**
- 9) **Streptokinase and tPA**
 - for ischemic priapism
- 10) **Baclofen** (20-40mg qHS)
 - γ -aminobutyric acid antagonist
 - potential role for “neurogenic” priapism

What are the potential treatments being studied in the management of priapism?

- reduction of pathologic changes } antioxidant therapy
- prevention of pathophysiologic mechanisms } PDE5 regulators

What are the AUA Guidelines for the management of priapism?

1) Evaluation

→ Hx

- duration of erection
- degree of pain
- previous priapism and tx
- use of drugs that may have precipitated the episode
- hx of pelvic, perineal, or genital trauma
- hx of sickle cell disease or other hematologic abnormality

→ P/E

- genital, perineal, & abdo exam } may reveal evidence of trauma or Ca

→ Labs

- CBC, retic count, Hgb electrophoresis
- psychoactive medication screening, urine toxicology
- cavernous blood gas testing } determine if ischemic or nonischemic

→ Imaging

- color duplex US
- penile arteriography

2) Management

→ Ischemic priapism

- treat all underlying disease (ex: sickle cell)
- therapeutic aspiration +/- irrigation, or ICI w/ phenylephrine
 - repeat as needed prior to surgical intervention
 - phenylephrine is α -agonist of choice
 - dilute to 100-500ug/cc, inject q3-5min for 1hr before calling tx failure
- kids & pts w/ severe CVS dz require smaller volumes or lower []
- observe pts for s/e of these agents
- BP/ECG monitoring are recommended in high risk pts
- shunt if ICI fails } Winter, Ebbehøj, El-Ghorab, Quackel, Grayhack, Barry
- oral systemic therapy not recommended

→ Nonischemic priapism

- corporal aspiration } diagnostic role only
- ICI of alpha blockade not recommended
- initial management is observation
 - discuss risk of spontaneous resolution, risk of tx-related ED, lack of significant consequences of delaying intervention
- selective arterial embolization w/ autologous clot or absorbable gels (non-permanent has lower ED rate – 5% vs 40%)
- ?methylene blue
- surgery is last resort } perform w/ intra-operative color duplex US

→ Stuttering priapism

- treat each episode as ischemic priapism
- trials of GnRH agonists or anti-androgens may be used
 - should not use in pts w/o full sexual maturation or adult stature
- consider ICI self-injection in pts that fail or reject systemic therapy
- other treatment options (“Viagra TAMED HIS Boner”)

List GU manifestations of sickle cell disease/trait.

—

→ **HUGE F'N PRIAPISM**

- **Hematuria** (dysmorphic RBCs) } M > F and L side 4x more than R
- **UTIs**
- **Glomerular disease** (MPGN, immune complex GN, etc) } leads to proteinuria
- **ED**
- **Frequency, polyuria, etc** (Nephrogenic DI)
- **Nocturnal enuresis**
- **Priapism**
- **RTA** (distal)
- **Infertility**
- **ARF**
- **Papillary necrosis**
- **Infarcts** (renal medulla, testicular)
- **Slow** (chronic) renal failure
- **Medullary RCC** (trait)

Chapter #27 – Androgen Deficiency in the Aging Male

DEFINITION

List the symptomatic manifestations of Androgen Decline in the Aging Male (ADAM)

- aka symptomatic late-onset hypogonadism (SLOH) or Testosterone Deficiency syndrome (TDS)
- gonadal function diminishes as part of normal aging } age-related hypoT
- may or may not include receptor sensitivity to androgens
- 1) ED
- 2) ↓'d libido
- 3) stable or slight decline in mood/cognition
- 4) fatigue
- 5) slight increase in sleep disturbances
- 6) hot flashes (vasomotor)
- 7) ↓'d QOL
- 8) ↓'d Hct
- 9) increased leptin production
- 10) stable LDL and HDL
- 11) increased fat mass
- 12) ↓'d muscle mass
- 13) ↓'d bone mass
- 14) hair and skin changes

What hormones are affected by the aging process?

- 1) ↓'d testosterone
- 2) ↓'d DHEA (regulation of vascular endothelium)
- 3) ↓'d GH (anabolic effects)
- 4) ↓'d melatonin (biorhythms and sleep)
- 5) ↓'d thyroxin
- 6) ↑'d leptin (regulates appetite and fat distribution; ?role in PCa)

EPIDEMIOLOGY OF HYPOGONADISM IN AGING

How common is ADAM/SLOH?

- increasing life expectancy in men } will become more common (on the rise)
- MMAS reported ~12 per 1000 person-yrs

PHYSIOLOGIC PRINCIPLES

What leads to the decrease in testosterone production associated with ADAM?

- aging hypothalamus likely produces less GnRH, leading to decreased LH and FSH
- decreased LH leads to decreased T production by the Leydig cells
 - Leydig cell numbers decrease in response
 - there may also be partial desensitization of Leydig cells to LH
- other factors can also affect Leydig cell production of T
 - neural influence from paraventricular nucleus of hypothalamus
 - ghrelin
 - thyroxine
 - retinoids
- decreased T (and lower FSH) also affects seminiferous tubules
- in addition to lower production, aging results in increased SHBG } less bioavailable T

Where are the sites of T production?

- testes } accounts for majority
- adrenal } produces weak androgens that function mainly as precursors
- brain } very small amounts that likely only serve local function

How is testosterone found in the body?

- ~2% free
 - ~38% bound to albumin
 - ~60% bound to SHBG
- \ accounts for bioavailable
/ testosterone
- SHBG levels increase with increasing age } T-SHBG can activate SHBG receptors in prostate and produce effects within the cell

List conditions that cause a rise in serum SHBG.

- aging
- cirrhosis
- hyperT₄
- use of anticonvulsants
- use of estrogen
- HIV infection

What is the metabolism of testosterone?

- 1) peripheral aromatization to 17 β -estradiol via aromatase
 - 2) reduction to DHT via 5AR
- catabolic products of T are mostly excreted in urine

How does testosterone work at the cellular level?

- T is transported through cell membrane and is converted to DHT
- T/DHT binds to the androgen receptor (AR)
 - AR is a ligand-inducible transcription factor
 - AR can also be activated by other factors such as protein kinase C
- binding of T/DHT to the inactive AR leads to translocation to the nucleus
- T/DHT binds to DNA
 - T has a stronger effect in those with shorter CAG repeat length
 - older men have less T and CAG repeats

What is the affect of aging on male androgens?

- 1) testes become less responsive to bioactive LH
- 2) decreased amplitude of circadian release of T
- 3) rising levels of serum SHBG

DIAGNOSIS

What is the criteria for the Dx of ADAM/SLOH?

- 1) symptoms + low or borderline low T
- 2) symptoms + normal T + response to therapeutic trial

What are the common presenting signs and symptoms of ADAM?

→ none are specific

→ symptoms

- loss of energy
- low libido
- dysphoria
- decreased ability to concentrate
- falling asleep after meals
- irritability

→ signs

- testicular atrophy
- decreased pubic hair
- decreased facial hair
- increased visceral fat
- loss of muscle mass
- osteoporosis

What is the recommended work-up for suspected ADAM/SLOH?

- 1) history } energy level, libido, visual field changes, galactorrhea, history of liver disease
 } meds, allergies, EtOH, smoking, drugs
 → must r/o depression
 } questionnaires (AMS, ADAM, etc)
- 2) physical } testis size, tumours
 } DRE
- 3) lab tests } **morning total T** (8-11am)
 → if low or borderline, repeat total and bioavailable T + LH + FSH
 → low T + high gonadotropins = primary hypogonadism in young men BUT IS NOT SO CLEAR IN OLDER MEN
 } consider LH, FSH, T4, prolactin if suspicious of secondary hypogonadism
- 4) trial of therapy x 3 months if symptomatic but hormonal screen is borderline/unclear

What are the 3 questionnaires developed to assess for hypogonadism in adult men?

→ good for screening but not for Dx

- 1) St Louis University's ADAM } 10 questions based on symptoms (Y or N)
- 2) Aging Male Survey (AMS) } 17 questions base on symptoms (likert scale)
 } 3 domains → psychological, sexual, somato-vegetative
 } minimum score is 17 and max is 85
- 3) Massachusetts Male Aging Survey (MMAS) } symptoms + epidemiologic findings

What are the 3 types of assays for measurement of total testosterone?

- 1) radioimmunoassay } poor accuracy and precision → should not be used
- 2) non-radioactive immunoassay kits
- 3) automated platform assays (chemiluminescent)

What are the 3 ways to calculate bioavailable testosterone?

- 1) free T measured by ultracentrifugal ultrafiltration or dialysis
- 2) **bioavailable T measured by ammonium sulfate precipitation } best**
- 3) calculated free T by measuring T and SHBG

TREATMENT OF SYMPTOMATIC LATE-ONSET HYPOGONADISM

What are the non-hormonal treatment options for ADAM/SLOH?

- lifestyle changes
 - stop smoking
 - stop alcohol abuse
 - improve diet
 - exercise
- counseling
 - for dysphoria
 - sexual dysfunction
- meds
 - bisphosphonates
 - anti-depressants

What are the advantages & disadvantages of the different testosterone supplementations?

	ADVANTAGES	DISADVANTAGES
1) oral	- easy to administer	- inactivated by “first-pass” effect through liver (need higher doses) - liver toxicity - risk of hepatic Ca
2) trans-buccal	- more physiologic rhythm	- inconvenient - gum-related S/Es (16%)
3) transdermal (best) → patch → gel	- more physiologic rhythm - no “first-pass” effect through liver - easy to use	- local skin symptoms - can be transferred to others
4) injectable im	- cheap	- not physiologic rhythm - frequent dosing - pain of injection - highest CV risk profile
5) pellet sc	- dosing only q3-6months	- not physiologic rhythm

List contraindications to androgen replacement therapy?

- “CHEAP Breasted Sluts” (or “CLUB HOP”)
 - CHF (class 3 or 4)
 - Hematocrit >50%
 - Elevated PSA (not investigated)
 - Abnormal DRE (not investigated)
 - Prostate Ca
 - Breast Ca
 - Sleep apnea (untreated)
 - severe LUTs (IPSS >19)

What are the main issues with T supplementation and PCa?

- does it increase the risk of PCa } maybe the opposite ... low levels of T may predispose to PCa
- does it cause localized PCa to grow } higher grade PCa may inhibit T secretion, so PCa may be higher in men with hypogonadism (who happen to be on T)
- can you give it to patients at high risk for PCa (eg ASAP) } unknown
- can you give it to patients treated for presumed localized PCa } unknown, safe in small studies

What alternative hormonal treatments are available for ADAM/SLOH, in addition to T?

- DHT } no aromatization
- 7 α -methyl-19-nortestosterone (MENT) } more potent, not reduced by 5AR, but can be aromatized to E2
- selective androgen receptor modulators (SARMs)

What are the effects of T supplementation on the aging male?

- 1) improved erections } improved NOS production and NO release
} even better if given with PDE5Is
 - 2) ↑'d libido
 - 3) possible improvements in cognition
 - 4) ↑'d energy
 - 5) decreased hot flashes
 - 6) improved QOL
 - 7) ↑'d Hct
 - 8) decreased leptin production
 - 9) decreased overall cholesterol } HDL decrease but also LDL decrease
 - 10) decreased fat mass
 - 11) ↑'d muscle mass
 - 12) ↑'d bone mass (BMD)
- if within physiologic range, T supplementation DOES NOT ↑ PROSTATE SIZE or WORSEN LUTS
→ RISK OF PCa STILL UNDETERMINED } may slightly increase PSA

RECOMMENDATIONS AND GUIDELINES

What is the position statement of the Sexual Medicine Society of North America on T supplementation?

- T supplementation is indicated for men who have **signs & symptoms of hypogonadism accompanied by subN serum T**
- T supplementation can provide some important health benefits
- T supplementation requires medical surveillance to r/o early side effects
- current evidence suggests T supplementation DOES NOT increase risk of heart disease or PCa
- T supplementation is NOT indicated in men who don't have hypogonadism

What is the recommended f/u for a man on T supplementation for ADAM/SLOH?

- prior to initiation of Rx
- CBC, LFTs and lipid profile
 - DRE + PSA
- TRUS Bx if abN PSA or DRE
- f/u while on T supplementation
- DRE + PSA q3months x 1yr, then q1yr
 - consider Bx if PSA increases by >0.5 ng/mL during first 6 months
 - periodic CBC, Total Testosterone, LFTs, cholesterol and lipid profiles
 - must watch for sleep apnea
- efficacy determined by clinical response rather than repeat T testing

List some EBM recommendations regarding T supplementation.

→ grade A

- symptomatic + biochemical evidence of ADAM should exist prior to Rx
- men with ED & libido problems are good candidates for Rx
- check lipid profile before and during Rx
- check DRE + PSA before and during Rx
- absolutely contraindicated in men with PCa, breast Ca or severe BOO
- check for polycythemia before and during Rx

→ grade B

- current T formulations are effective & safe
- goal is to bring serum T levels to physiologic range (not supraphysiologic)
- no evidence for or against the need for circadian rhythm
- should monitor for aggressiveness & hypersexuality

→ grade C

- age is NOT a limiting factor to starting Rx
- combined Rx with PDE5-I may be synergistic
- sleep apnea may get worse on Rx so should be reassessed

→ grade D

- Rx can be started after “a prudent interval” in men w/ treated PCa

List common drugs that inhibit GnRH production?

- | | |
|------------------|---------------------|
| - TCAs | - GnRH agonists |
| - progesterone | - estrogens |
| - opioids | - reserpine |
| - phenothiazines | - cocaine |
| - ketoconazole | - anabolic steroids |
| - aldactone | - amiodarone |
| - thiazides | - anti-androgens |
| - cimetidine | |

- excitement } engorgement of the vaginal mucosa, causing thickening of the vaginal walls and transudation of fluid into the vagina
- } vasocongestion & engorgement
- plateau } labia minora become congested and enlarged
- } clitoris retracts under clitoral hood + lengthening of vagina, skin flushing
- orgasm } peak of physiologic & psychological pleasure
- } rhythmic contraction of outer 1/3 of vaginal vault, uterus
- } increase in BP, RR, HR, pelvic thrusts
- resolution } slow disappearance of pelvic & vulvar congestion
- } return of vulvar structures and breasts to normal size

DIAGNOSIS

What is the work-up for female sexual dysfunction?

- 1) history } medical and surgical hx, meds, allergies
 - chronic medical illnesses (DM, anemia, CRF, etc)
 - neurologic diseases (SCI, MS, disc disease)
 - endocrine disorders (hypogonadism, hyperprolactinemia, thyroid, etc)
 - atherosclerotic RFs (cholesterol, HTN, DM, smoking, FmHx, etc)
 - pelvic/perineal/genital trauma
 - gyne hx (children, abortions, abN pap smears, STDs, PID, endometriosis, fibroids, menopause, hysterectomy, etc)
 - urologic hx (incontinence, recurrent UTIs, IC, etc)
 - surgical hx (laminectomy, colon/anal sx, vascular sx, etc)
 - psychiatric hx
- } sexual hx
 - description of sexual problem (symptoms, timing, alone, with partner, history of sexual function, treatments to date, etc)
 - questionnaires
- } psychosocial hx (or consult)
 - abuse and trauma
 - sexual beliefs
 - emotional concerns
 - interpersonal relationships
- 2) physical exam } general physical
- } genital-focused exam
 - inspection of anatomy } clitoris, labia, hymen, vestibular glands
 - clitoral phimosis → genital atrophy
 - vestibular adenitis
 - palpation } single digit vaginal exam
 - vaginismus
 - may include speculum exam and bimanual exam
- } +/- neurologic exam
- 3) lab tests } vaginal fluid tests
 - pH } normal is 3.5 – 4.5
 - } if >4.5, consider bacterial vaginitis, vaginosis, atrophic vaginitis
 - wet mount + culture } normally, lactobacilli is predominant organism
 - } clue cells = bacterial vaginosis (trichomonas, candida)
 - } ↑'d parabasal epithelial cells = atrophy or inflammation
 - } >1 WBC/epithelial cell = trichomonas, yeast, STD, atrophy, PID
- } no routine blood tests recommended
 - hormonal tests PRN } DHEAS, androstenedione, T, SHBG, DHT, estradiol, estrone, LH/FSH, prolactin, TSH

What organisms are part of the normal vaginal flora?

- **lactobacilli (most common)**
- GBS
- *E coli*
- Gardnerella
- enterococcus

What other specialized tests may be used to assess female sexual dysfunction?

- 1) vascular tests } duplex Doppler U/S
 - if internal iliac-pudendal arterial insufficiency is suspected
 - can also be used to assess vaginal, clitoral, and labial blood flow during arousal
- 2) MRI } tissue changes in pelvic genital area & brain
 - } anatomic relationships of genital structures
- 3) neurologic testing } quantitative sensory testing (QST)
 - if neurologic pathology suspected } SCI, MS, lumbar radiculopathy, peripheral neuropathy, etc

TREATMENT

Pre-menopausal women

What is the role of estrogens & progesterones for PRE-menopausal female sexual dysfunction?

- 1) if regular menstrual cycles + ovulation } NO ROLE
- 2) if abN menses + amenorrhea/dysmenorrhea/menorrhagia } MAY BENEFIT FROM HORMONE RX
 - different forms of estrogen/progesterone may adversely influence sexual function

How do OCPs affect sexual function?

- decreased libido
- decreased female-lead sexual activity
- decreased sexual intercourse and sexual enjoyment
- **occurs due to decreased androgen levels**
 - 1) direct inhibition of androgen production in ovaries
 - 2) increased hepatic synthesis of SHBG

List conditions/factors that cause decreased testosterone levels in PRE-menopausal women

- aging (gradual, not like estrogen/progesterone and menopause)
- hyperprolactinemia
- adrenal insufficiency
- cushing's disease
- excess glucocorticoids (endogenous or exogenous)
- OCP

Where is testosterone produced in women?

- ovaries + adrenals (50%)
- peripheral conversion from DHEA and androstenedione (50%)

What are the signs & symptoms of androgen insufficiency in women?

- dysphoric mood
- persistent fatigue
- **decreased libido**
- decreased pleasure
- decreased vaginal lubrication
- bone loss
- decreased muscle strength
- changes in memory/cognition

What is the role of androgens in PRE-menopausal female sexual dysfunction?

- **may improve sexual desire, libido, pleasure, orgasm + local vaginal physiologic fxn**
- currently limited data on long-term safety } more studies needed

What are the potential side effects of androgen therapy?

- acne
- balding
- hirsutism
- deepening of voice
- cliteromegaly
- polycythemia
- hepatotoxicity
- reduced HDL
- increased risk of breast Ca
- ?risk of endometrial Ca

Peri- and Post-menopausal women

How does sexual dysfxn in PERI- & POST-menopausal women differ from pre-menopausal women?

- more common to have sexual dysfunction
- less likely to be reversible
- more likely to be progressive
- less likely to be situational

What changes occur in the genital tissues as a result of menopause?

- estrogens are required for genital tissue structure and function
- vaginal atrophy, dryness, friability
- change to alkaline vaginal pH } change in flora that increases risk of yeast infections
- diminished vaginal sensation
- phimotic clitoral hood
- glans clitoral atrophy
- shrinkage of labia minora

What are the effects of estrogen/progesterone on peri- and post-menopausal women?

- systemic
 - decreased hot flushes, night sweats, sleep disturbances
 - improved body image, mood, sexual desire, orgasm
 - improved local vaginal symptoms
- local
 - improved vaginal lubrication and vaginal dryness
 - improved dyspareunia

What are the effects of androgens on peri- and post-menopausal women?

- DHEA
 - increased total testosterone
 - increased skin hydration
 - improved bone density
 - improved libido
- testosterone
 - improved sexual activity
 - improved pleasure and orgasm
 - improved arousal
- not yet approved for clinical use in women } more studies needed

What non-hormonal medication has been used for peri- & post-menopausal sexual dysfunction?

- dopamine agonists } **mainly a central affect**
 - } improves sexual motivation, arousal, desire, orgasm, etc
 - eg apomorphine, amantadine, bupropion
- vasodilators } effects on clitoris, vaginal epithelium, etc
 - } improved arousal, orgasm, frequency of intercourse
 - eg **PDE5-I** } **ideal for sexual arousal d/o and psych meds-induced sexual dysfunction**
 - } adequate hormonal milieu essential for benefit

What are the causes of dyspareunia?

- physical } endometriosis, pelvic adhesions, pelvic tumours, abN GI/GU tract, coital posture, retroverted uterus, intact hymen
- inflammatory causes } introital fissures, urethritis, vaginitis
- lack of lubrication
- psychological } anxiety, fear

What are the causes of female sexual dysfunction related to sexual pain?

- clitoris, prepuce, frenulae } phimosis/balanitis (fungal, HSV, lichen sclerosus or planus)
 - Rx → topical estrogen/testosterone +/- antifungals, acyclovir, clobetasol steroid
 - dorsal slit
- } preputial infections (infected sebaceous cyst)
 - Rx → Abx, sitz baths
 - I&D
- } traumatic neuropathy (birth, C-section, cycling, pelvic #, etc)
 - Rx → gabapentin
- } frenular fibroepithelioma
 - Rx → local excision
- urethral meatus, urethra, BN, skene's glands } urethral prolapse (pain + urgency except with masturbation)
 - Rx → systemic/topical estrogen
 - excision of prolapse
- } skene's gland adenitis
 - Rx → systemic/topical estrogen
- urethritis, UTIs, IC } urologic conditions (recurrent urethritis/UTIs, urethral diverticula, cystocele, ureteral stones, endometriosis of ureter and/or bladder)
 - } gynecologic conditions (yeast infections, uterine prolapse, etc)
- vulva } lichen sclerosus/lichen planus
 - Rx → clobetasol steroid
- } Bartholin's gland cyst
 - Rx → Abx, sitz baths
 - marsupialization
- vestibule } generalized vulvodynia
 - Rx → education, hygiene, pelvic floor PT, treatment of concomitant depression, gabapentin, amitriptyline
- } **vulvar vestibulitis syndrome**
 - **most likely cause of dyspareunia in F <50yrs**
 - HPV, irritant oxalate, abN immunology, psych, abN hormonal milieu
 - Rx → education, PT, biofeedback, topical estrogen, topical lidocaine, TCAs, gabapentin
 - excision of vestibular adenitis or complete vulvar vestibulectomy
- } redundant labia minora
 - Rx → surgical reduction
- vagina } atrophic vaginitis (parabasal cells, increased WBCs, no lactobacilli, alkaline pH)
 - Rx → topical estrogen
- pelvic floor disorders

What are the potential complications of surgery for vulvar vestibulitis syndrome?

- bleeding/hematoma
- infection
- increased pain
- Bartholin's duct cyst formation
- vaginal stenosis
- scarring
- wound dehiscence

Intratubular Germ Cell Neoplasia: CIS of the Testis

What is the significance of testicular CIS (ITGCN)?

- develops from fetal gonocytes
- **regarded as precursor lesion for GCTs → except spermatocytic seminoma**
- **debatable** } found in 0.8% of men → same prevalence as testis cancer
 - } contralateral GCT risk is ~5% → which is same as risk of CIS in contralateral testis
 - } **50% with CIS on Bx for infertility had invasive dz w/in 5yrs** (Skakkebaek '82)
- histologically see seminiferous tubules with SCO & malignant germ cells in single row along membrane
- **usually found evenly distributed throughout testis**

What are the RFs for developing testicular CIS?

- 1) history of testicular cancer (5%)
- 2) extragonadal GCT (40%)
- 3) UDT (3%)
- 4) contralateral testis with unilateral testicular cancer (5%)
 - **Bx of contralateral testis NOT RECOMMENDED for all patients with GCTs**
- 5) atrophic contralateral testis with unilateral testicular cancer (30%)
- 6) somatosexual ambiguity (25-100%)
- 7) infertility (~1%)

How do you diagnose testicular CIS?

- no markers and U/S unreliable
- **Bx is gold standard → needle just as good as open**

What is the management of testicular CIS?

- depends on age, laterality of CIS, associated atrophy, and philosophy of surgeon
 - Europe (esp Scandinavia) } low dose RADs (18-20Gy)
 - rendered infertile
 - N. America } observation vs orchiectomy vs RADs
- CHEMO is fairly ineffective
- role of contralateral testis Bx is controversial } Europe tends to do Bx because they tend to Rx up front

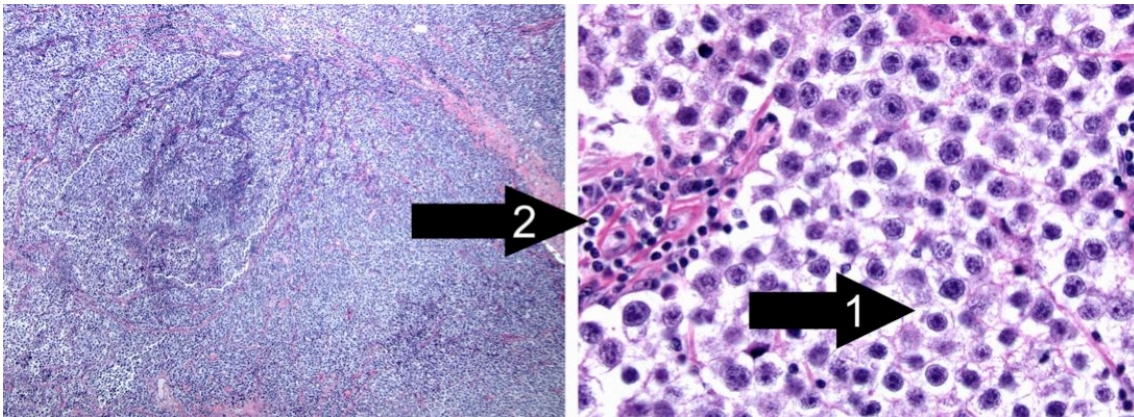
List reasons not to Bx the contralateral testis to r/o CIS.

- prevalence of CIS similar to prevalence of testis Ca (0.8%)
- contralateral GCT risk is same as risk for CIS (5%)
- CIS has protracted course
- finding CIS may lead to more morbid therapy
- even if 2nd contralateral GCT develops, patients respond well to treatment

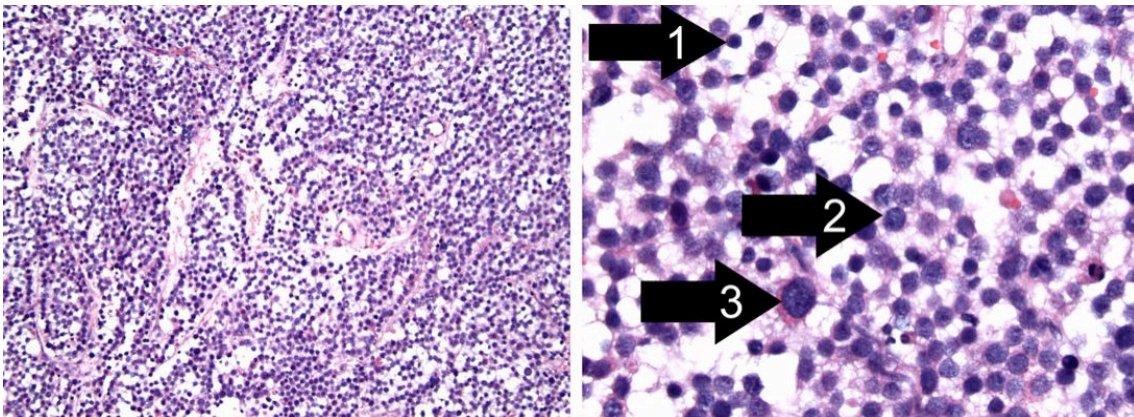
Seminoma

List the subtypes of seminoma (30-60%)?

- 1) **classic** → **85% of seminomas**
 - men in 30's (up to 50's) ... rare in kids
 - **10-15% have syncytiotrophoblastic elements (+ve β HCG)**
 - slower growing than NSGCTs
 - large cells (similar size) w/ clear cytoplasm + densely staining nuclei } “fried egg”
 - lymphocytic infiltrate } → like clear cell RCC
 - 2) **spermatocytic** → 10%
 - resemble different phases of maturing spermatogonia
 - most occur in men >50yrs
 - rare to be associated with NSGCT & never see elevated markers
 - **NOT associated w/ UDT nor CIS**
 - **metes is very RARE ... good prognosis**
 - see 3 different size cell types with deeply pigmented cytoplasm & rounded nuclei
 - 3) **anaplastic** → 5% } trend towards eliminating this subtype classification
 - aka “seminoma with high mitotic index” } may resemble embryonal NSGCT
 - men in 30's (up to 50's) ... rare in kids
 - **more aggressive** } higher mitotic activity, higher rate of local invasion, increased rate of mets, **higher rate of bHCG production**
 - increased mitotic activity, nuclear pleiomorphism, and cellular anaplasia
- **NEVER has elevated AFP ... 10-15% have elevated bHCG ... 90% have PLAP**



→ **CLASSIC SEMINOMA** } “fried egg” appearance (1) with lymphocytic infiltrate (2)



→ **SPERMATOCYTIC SEMINOMA** } 3 different cell types with NO lymphocytes

How can immunohistochemistry be used to differentiate seminoma from embryonal carcinoma?

- anaplastic seminoma especially resembles embryonal NSGCT
- most seminomas are **PLAP +ve**
- most seminomas are **c-kit +ve**
- most seminomas are **CD30 -ve**

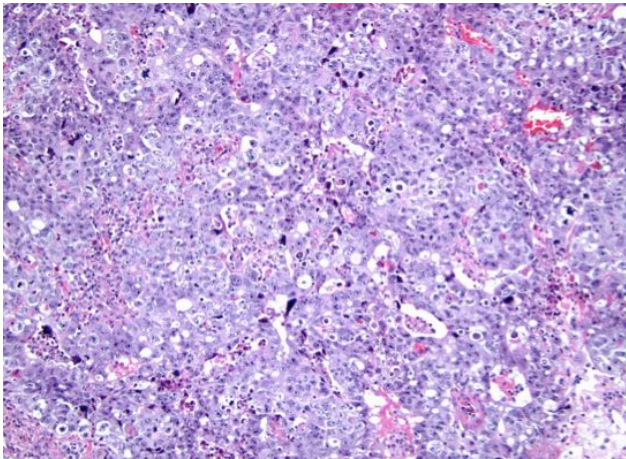
Nonseminomatous GCTs

→ “A-YET B-SEC”

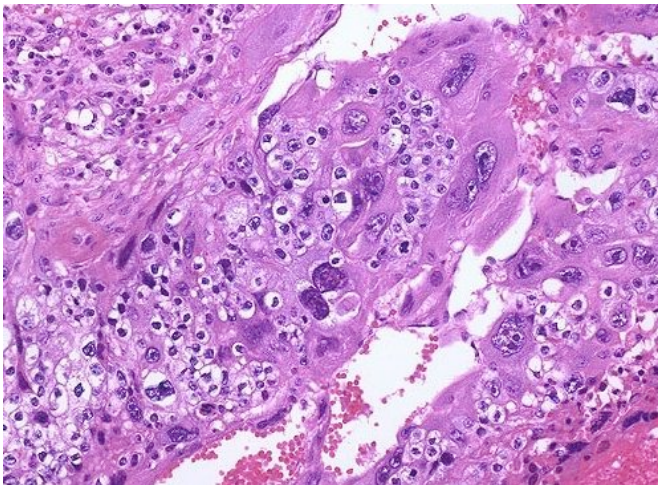
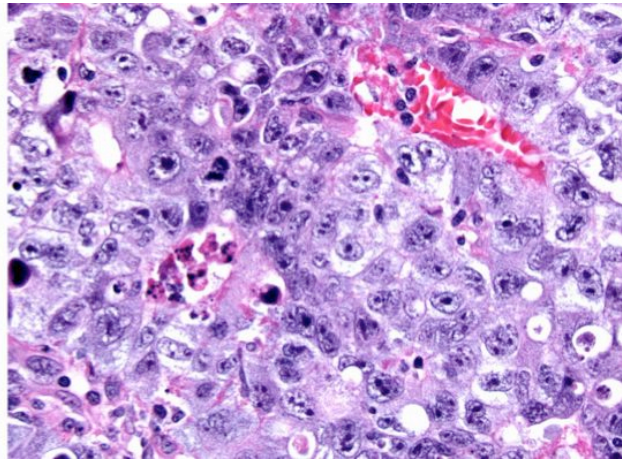
- 1) embryonal (3-5%)
 - usually small, rounded, irregular mass invading locally
 - greyish-white with areas of necrosis/hemorrhage
 - distinctly malignant epithelioid cells arranged in glands or tubules
 - **>40% embryonal is risk factor for mets (least differentiated)**
 - **pure embryonal rarely has elevated markers**
 - often have syncytiotrophoblastic elements (**bHCG +/- AFP**)
- 2) choriocarcinoma (1%)
 - size often depends on extent of hemorrhage
 - greyish-white with **central hemorrhage**
 - often presents with **mets with relatively small testicular lesion**
 - contains **syncytiotrophoblasts (bHCG) AND cytotrophoblasts**
 - pure chorio ALWAYS mets as pure chorio
 - **high elevated bHCG but NEVER AFP**
- 3) teratoma (5-10%)
 - usually large, lobulated, and nonhomogeneous (+ cartilage on micropathology)
 - more common in kids than adults
 - contain different cell layers in various stages of maturation and differentiation
 - mature elements → benign structures from ectoderm/entoderm/mesoderm
 - immature elements → undifferentiated primitive tissue from ectoderm/entoderm/mesoderm (PNET)
 - may get malignant differentiation (5-10%)
 - teratoma component of metastatic GCT is chemo/radio-resistant } RPLND role
 - **elevated AFP in 20-25% } these are not pure teratoma**
- 4) yolk sac (1%)
 - very common testis tumour in kids (mature teratoma most common)
 - in adults, usually in mixed form
 - when pure usually yellowish, mucinous, homogeneous
 - often contain **EMBRYOID BODIES** that resemble 1-2 week old embryos
 - has syncytiotrophoblasts and cytotrophoblasts
 - **Shiller-Duval bodies**
 - similar to embryonal cell on gross path
 - microscopic pattern is a) microcystic, b) endodermal sinus, or c) solid
 - slow-growing and 80% confined to testis at time of Dx
 - **AFP elevated in 90%**
- 5) mixed (60%)
 - most common GCT
 - **embryonal + yolk sac + teratoma + syncytiotrophoblasts is MOST COMMON**
 - teratoma with mets is mixed until proven otherwise (80%) → usually embryonal
 - even with seminoma in primary, treated as NSGCT
 - almost never has seminoma in mets
 - **usually elevated AFP (yolk sac) and bHCG (syncytiotrophoblasts)**

What is another name for yolk sac tumour?

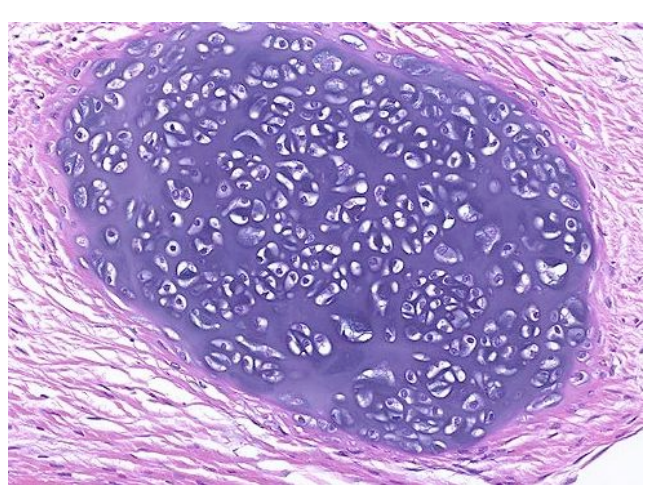
- endodermal sinus tumour
- adenocarcinoma of the infantile testis
- juvenile embryonal carcinoma
- orchioblastoma



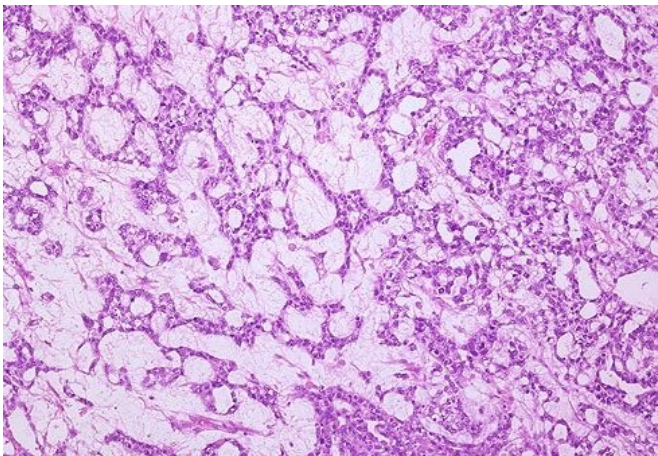
→ EMBRYONAL CARCINOMA (looks nasty)



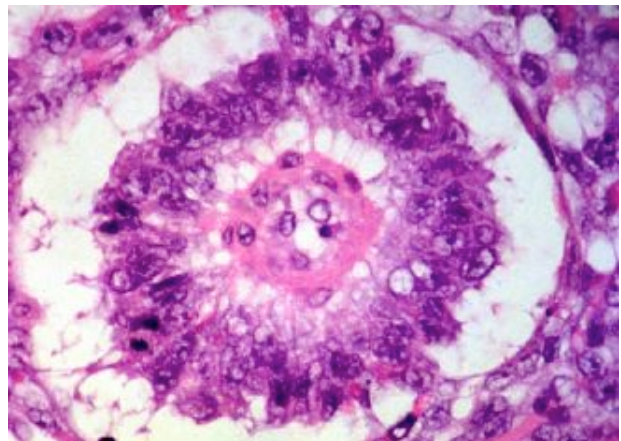
→ CHORIOCARCINOMA NSGCT



→ MATURE TERATOMA NSGCT (cartilage)



→ YOLK SAC NSGCT (little cellularity – AML-esque)



→ YOLK SAC NSGCT } Schiller-Duval Body

Epidemiology of GCTs

What is the incidence of testicular GCTs?

- 1 in 500 → higher in Europe (~5-8%)
- less common among Blacks and Asians .. highest among Scandinavians, Germans, Kiwis
- higher incidence with higher socioeconomic status

Why are testicular tumours associated with high cure rates?

- 1) accurate serum markers
- 2) radiosensitive
- 3) chemosensitive
- 4) rapid rate of growth
- 5) predictable, systemic pattern of spread
- 6) occurs in young healthy men
- 7) capacity to differentiate into histologically more benign entities

What are the RFs for developing testicular cancer? } } } “ His Cancer SURFACED”

- 1) HIV
 - 2) Cancer (contralateral testis)
 - 3) Sexual ambiguity } streak gonads, AIS, atrophy
 - 1) UDT } ?decreased risk if fixed before 1yr (before 13yrs NEJM '07)
 - 3) Race → less in Blacks and Asians ... higher in whites and Jews
 - 8) Family Hx
 - 2) Age
 - 7) CIS
 - 6) Estrogen exposure in utero
 - 4) Dysgenetic testes
- NO GENETIC PREDISPOSITION

At what age do testicular GCT's commonly present?

- trimodal peak incidence → <10yrs (usually benign)
→ 20s-40s (most common)
→ >60s
- seminoma rare before 10yrs & after 60yrs } spermatocytic seminoma occurs most commonly after 50s
- yolk sac very common in kids but also common in mixed tumours in young adults
- benign, pure teratoma most common in kids but also common in mixed tumours in adults

Is testicular cancer more common on one side versus another?

- slightly more common on R → R has slightly higher incidence of UDT
- **2-10% bilateral** → usually metachronous with similar histology
→ **seminoma most common bilateral histology**

What is the significance of testicular microlithiasis?

- found in 50-70% of men with NSGCTs → also found with CIS
 - classically, bilateral evenly distributed bright echoes
 - if incidental finding, no role for testis Bx, orchiectomy, etc
 - consider Bx only if:
 - 1) focal, clumped + unilateral mass
 - 2) testis CA + TM in contralateral testis
 - 3) TM in infertile man, UDT, atrophic testis
- \ new data shows NO ↑'d risk
/ of testis Ca and that
/ prevalence in N men
/ is ~7% (military data)

What is the DDX of testicular microlithiasis?

- “ROC FIGSS”
- RADs
 - Orchitis
 - Chemo (post)
 - Fibrosis
 - Infarction
 - Granuloma
 - Scar
 - Sarcoidosis

List diseases associated with testicular microlithiasis.

- “DICK And NUT In V”
- Dysgenetic testis
 - Infertility
 - Cancer or CIS
 - Klinefelter's
 - AIDS
 - Neurofibromatosis
 - UDT
 - Torsion
 - Infarcted testis
 - Varicoceles

Etiology

What are the causes of testicular cancer?

- 1) congenital
 - UDT → 7-10% of men with testis Ca have hx of cryptorchidism
 - abN germ cell morphology, elevated temp, interference w/ blood supply, endocrine dysfunction, and gonadal dysgenesis
 - 3-15X higher risk } lower if fixed before 1yr (NEJM '07 13yrs)
 - 5-10% develop testicular Ca in N contralateral, descended testis
- 2) acquired
 - trauma → NO
 - hormones → DES exposure to mom puts sons at slightly increased risk (Leydig)
 - atrophy → nonspecific or mumps-associated atrophy might be a risk factor

Patterns of Spread of Germ Cell Tumours

What is the natural history of GCTs?

- **almost 60% of men with NSGCTs present with disseminated disease**
- **only ~30% of men with seminomas present with disseminated disease**
- involvement of cord or epididymis can lead to pelvic LN mets (external iliac, internal iliac)
- all testis GCTs are considered malignant
 - except teratoma in infants } can be regarded as benign
 - retroperitoneal teratoma often grows and is only controlled by excision
- extension through tunica albuginea is usually at testicular mediastinum
- **most GCTs spread via lymphatics, but chorio almost always spreads hematogenously**
- 2yr survival is old end-point/benchmark ... now should be 5yrs ... longer f/u after chemo because late relapse noted up to 10yrs later

What is the drainage of the **R testis**?

- mainly **inter-aortocaval nodes**
- **can see R-to-L cross-over } can cross up and over to L renal hilar area**

What is the drainage of the **L testis**?

- mainly **para-aortic nodes**
- uncommon to see L-to-R cross-over } can occur

What is the drainage from the retroperitoneal LNs?

- cephalad to cisterna chyli, thoracic duct, and supraclavicular LNs (usually left)
- can spread retrogradely to common, external, and inguinal LNs } if ++ bulky disease

When do you see inguinal LN mets with testicular cancer?

- 1) retrograde spread from massive retroperitoneal nodes
- 2) scrotal involvement (T4)
- 3) previous scrotal or inguinal surgery

What is the likelihood of distant mets without retroperitoneal disease?

- **5% distant failure despite negative RPLND**

What is the doubling time of GCTs?

- 10-30 days (except for seminoma ... slower)

Clinical Manifestations

What are the signs & symptoms of testicular cancer?

- usually asymptomatic other than nodule or painless mass in testis
- dull ache or heavy sensation in lower abdomen, back, anal area, or scrotum
- acute scrotal pain → 10%
- infertility
- manifestation of mets → 10%
 - neck LNs
 - cough/dyspnea
 - GI symptoms
 - lumbar back pain
 - bone pain
 - central or peripheral nerve symptoms
 - unilateral or bilateral leg edema
- gynecomastia → 5%
 - systemic endocrine manifestation (eg β HCG)

What are the physical exam findings of testicular cancer?

- hard nodule or enlarged testis
- spread to epididymis or cord → 10-15%
- abdominal mass
- supraclavicular LNs
- gynecomastia (even with normal β HCG)

DDX

What is the DDX of a testicular mass?

- torsion
- epididymitis
- epididymo-orchitis
- hydrocele
- hernia
- hematocele
- spermatocele
- syphilitic gumma

Scrotal U/S

What are the classic findings on scrotal U/S that make testicular cancer likely?

- **hypoechoic** mass (black on U/S) within tunica albuginea
- debatable as to whether more likely malignant or benign

CLINICAL STAGING

Staging Systems

What are the essential aspects of testicular cancer staging?

- pathological T stage
- lymph node status on imaging
- metastatic disease on imaging
- serum markers

How accurate are staging techniques?

- 10-15% of men with clinical stage 1 disease harbour undetected retroperitoneal disease
- 5-10% of men with clinical stage 1 disease fail extranodally even after RPLND

What is the recommended work-up for testicular cancer?

- 1) History
 - local symptoms } location, onset, duration, pain or painless, radiation of pain, LUTs, STDs
 - metastatic symptoms } neck mass, cough, dyspnea, lumbar back pain, bone pain, leg edema
 - gynecomastia (from increased β hCG)
 - RFs ("His Ca SURFACED") } HIV, Ca in other side, sexual ambiguity, UDT, race, FmHx, age, CIS, maternal estrogen in utero, dysgenetic testes
 - other RFs } recent instrumentation, risky sexual encounters, travel hx, TB exposures, UTIs,
 - PMHx, meds, allergies, EtOH, smoking, drugs
- 2) Physical Exam
 - general appearance, vitals
 - neck & chest exam } supraclavicular LNs
 - abdo exam } masses, DRE
 - genital exam } mass, size, contour, consistency, testicular vs paratesticular, large varicoceles
- 3) lab work
 - tumour markers } AFP, β HCG, LDH
 - CBC, lytes, creatinine, Ca profile, LFTs, PTT, INR
- 4) imaging
 - CXR
 - CT abdo/pelvis } gold standard but not perfect because can't detect micromets
 - MRI is no better than CT for abdomen
 - testicular lesion is hypointense on T2
 - brisk and early enhancement after Gadolinium
 - **good for vascular involvement**
 - CT chest } if CXR is abN, if symptoms suggestive of mets, or +ve retroperitoneal disease on CT
 - **risk of chest disease is <5% if abdo CT is normal**
 - PET scan } often used to evaluate retroperitoneum after chemo (uptake of FDG)
 - like CT, can't detect microscopic nodal disease
 - can't differentiate teratoma from fibrosis } no role for NSGCT post-chemo mass
 - **small role EXCEPT in post-chemo SEMINOMA residual mass**
- 5) miscellaneous
 - discuss sperm banking if suspicious for testis Ca
- 6) surgery } open inguinal radical orchiectomy

What is the 2008 AJCC TNMS Staging system for testicular cancers (updated from '97) ?

→ 60% of all men with testicular GCTs present with stage 1 disease

→ stage 1 more common with seminoma (~70%) than NSGCTs (30%)

PRIMARY TUMOUR (pT)

pT0	no evidence of primary tumour
pTis	ITGCN (CIS)
pT1	limited to testis & epididymis without LVI → can invade tunica albuginea, but not tunica vaginalis
pT2	limited to testis & epididymis + LVI or extending into tunica vaginalis
pT3	invades spermatic cord +/- LVI
pT4	invades scrotum +/- LVI

CLINICAL REGIONAL LNs (cN)

N0	no regional LN mets
N1	LN ≤2cm or multiple LNs all <2cm
N2	LN 2-5cm or multiple LNs all 2-5cm
N3	LN >5cm

PATHOLOGIC REGIONAL LNs (pN)

pN0	no regional LN mets
pN1	LN ≤2cm or ≤5 LNs all <2cm
pN2	LN 2-5cm or >5 LNs all <5cm or evidence of extranodal extension
pN3	LN >5cm

DISTANT METS (M)

M0	no distant mets
M1a	non-regional nodal or lung mets
M1b	distant mets

SERUM TUMOUR MARKERS (S) }}} after orchiectomy

S0	all markers normal
S1	LDH <1.5x N + AFP <1000 + βhCG <5000
S2	LDH 1.5-10x N + AFP 1000-10,000 + βhCG 5000-50,000
S3	LDH >10x N + AFP >10,000 + βhCG >50,000

SUMMARY

T1 = Stage 1a \ potential to observe in
T2-T4 = Stage 1b / this group

N1 = Stage 2a \ RP therapy vs
N2 = Stage 2b / chemo

N3 = Stage 2c \ good-risk group
M1aS1 = Stage 3a / (good + intermediate)

S2 = Stage 3b \ poor-risk group
M1bS3 = Stage 3c / (no poor risk for seminoma)

What is the AJCC Stage Grouping system for testicular cancer?

Stage Grouping

Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	PT3	N0	M0	S0
	PT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/Tx	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Findings at Orchiectomy

What are the important findings at orchiectomy?

- 1) histologic subtype } percentage of each subtype
- 2) T stage with size
- 3) presence of LVI
- 4) presence of ITGCN

What are the indications to perform inguinal Bx on contralateral testis?

- for high-risk patients only } **risk of metachronous tumours is only ~2-3%**
- 1) suspicious U/S for intratesticular abN'ities
 - 2) UDT
 - 3) marked atrophy
 - 4) focal, clumped microlithiasis

Tumour Markers

What are the different types of tumour markers?

- 1) oncofetal substances associated with embryonic development
 - **AFP** → **trophoblasts (early embryo)**
 - **βHCG** → **syncytiotrophoblasts (placenta)**
- 2) cellular enzymes
 - LDH
 - PLAP

What is the significance of AFP and GCTs? } } } “A-YET”

- produced by **trophoblasts** from fetal **yolk sac**, liver, and GI tract
- highest at 12th-14th weeks of gestation, declines to low levels at 1yr after birth
- **T_{1/2} is 5-7 days** } aFp for Five days
- **Yolk sac**
- pure **Embryonal** (rare)
- **Teratocarcinoma**
- **NEVER pure chorio**
- **NEVER pure seminoma**

What is the DDx of elevated AFP?

- | | |
|-----------------|--------------------------------|
| - testis Ca | - benign liver disease |
| - liver Ca | - ataxia-telangiectasia |
| - pancreatic Ca | - tyrosinemia |
| - stomach Ca | - pregnancy |
| - lung Ca | |

What is the significance of β HCG and GCTs? } } } “B-SEC”

- produced by placenta (**syncytiotrophoblasts**) during normal pregnancy
- **T_{1/2} is 24-36 hours**
- 10-15% of **Seminoma** → usually low bHCG though
- ~50% of **Embryonal**
- **ALL Choriocarcinoma**
- **NEVER in pure yolk sac**

What is the DDx of elevated bHCG?

- | | | |
|-----------------|---------------------|--|
| - testis Ca | - kidney Ca | - marijuana/cigarette smokers |
| - liver Ca | - bladder Ca | - hypergonadatropic hypogonadism |
| - pancreatic Ca | - breast Ca | (cross reacts with α-subunit of LH) |
| - stomach Ca | - cirrhosis | - pregnancy |
| - lung Ca | - IBD | |

What is the significance of LDH and GCTs?

- 4 isoenzymes
- high levels in smooth, cardiac, and skeletal muscles, liver, kidney, brain
- measure of tumour burden
- useful marker for surveillance of patients with advanced seminoma

What is the significance of PLAP and GCTs?

- fetal isoenzyme
- **elevated in seminoma**

What is the significance of GGTP and GCTs?

- hepatocellular enzyme
- **elevated in seminoma**

How often are tumour markers elevated?

- | | |
|---------------------------------------|---|
| - NSGCT → 50-70% elevated AFP | \ } 10-15% have normal markers / |
| → 40-60% elevated bHCG | |
| → ~90% have elevations of one or both | |
| - seminoma → AFP is NEVER elevated | |
| → 10-15% have elevated bHCG | |

What is the role of tumour markers post- treatment?

- if markers still elevated after orchiectomy (and no other cause for elevated markers), then likely systemic mets not just retroperitoneal disease
- if markers decline slower than expected (as per half-lives), then likely residual disease
- rate of marker decline after treatment (Sx, rads, chemo) is proportional to the decrease in tumour burden and viability
- serologic relapse may often precede clinical detection
- elevated markers after treatment of metastatic disease indicates incomplete response
 - therapeutic lag after chemo and rads makes expected rate of decline slightly unclear
- **10-15% of patients that have normalization of markers after chemo for bulky metastatic disease still have viable tumour found on RPLND**

What is the prognostic value of tumour markers?

- degree of AFP and bHCG elevation is proportional to amount of tumour burden
- elevation of bHCG, LDH, or both and # of mets are important prognostic factors for survival

GCTs: Principles of Treatment

Why is there a push to decrease the total therapeutic burden for testicular cancer?

- 1) accuracy of clinical staging
- 2) ability to recognize failure early
- 3) high probability of successful Rx of failures

What is the role of radical orchiectomy?

- provides histologic diagnosis
- provides T staging
- virtually 100% local control
- results in cure for patients with tumour confined to testis (70% seminoma, 30% NSGCTs)
- minimal morbidity and virtually no mortality

What is the management of scrotal violation or tumour spillage at time of orchiectomy?

- 1) NSGCT } excision of retained spermatic cord remnant + scrotal scar
- 2) seminoma } Rads to groin + ipsilateral hemiscrotum (implantation almost never seen)
 - push towards doing less } hemiscrotectomy and inguinal LN dissection NOT recommended
 - **doesn't change rate of systemic recurrence just changes pattern of recurrence**

What is the general treatment differences between N America & Europe? } } } NO LONGER TRUE .. more in-line

- | | |
|-------------------|-------------------|
| → N America | → Europe |
| - seminoma → rads | - seminoma → rads |
| - NSGCTs → RPLND | - NSGCTs → rads |

What are the indications for partial orchiectomy?

- 1) organ-confined, nonpalpable tumours <2cm (<25% of testis) and;
 - a) solitary testis
 - b) bilateral disease
- 2) suspected benign disease } incidental non-palpable small eg sarcoidosis (still do inguinal approach)
 - NOT for patients with impaired endocrine fxn pre-op
 - if evidence of CIS in residual tissue, will need RADs (20Gy) } will be infertile but T function is ok

What are the principles of partial orchiectomy?

- inguinal approach with occlusion of spermatic cord
- tumour identification by palpation or U/S
- send tumour and Bx of tumour bed to pathology for frozen section
- cold-ischemia likely not req'd (torsion analogy) and RADS of little benefit for assoc'd ITGCN
- bank semen pre-op

Seminoma

What is the pattern of presentation of seminoma?

- **75-80% present with stage 1 (confined to testis)**
- 10-15% have retroperitoneal disease
- ~5-10% have distant mets
- seminoma deaths usually assoc'd with **liver/lung (75%), bone (50%), and brain (25%)** mets
- **1/3 of those that die with pure seminoma harbour NSGCT elements in mets**

What are the RFs associated with relapse of SEMINOMA?

- | | |
|-----------------------------------|---|
| 1) primary tumour >4cm | } strength of risk stratification
NOT as strong as with NSGCTs |
| 2) rete testis involvement | |
| 3) LVI | |
| 4) elevated bHCG | |
| 5) anaplastic subtype | |

What is the management of STAGE 1A/B SEMINOMA?

- 1) spermatocytic → no further therapy
 - 2) classic and anaplastic
 - a) no RFs and reliable → SURVEILLANCE (maybe even for +RFs)
 - need long-term f/u d.t. late recurrences (10yrs -Jewett)
 - **15-20% RELAPSE RATE but overall survival same**
→ relapse usually w/in 12-18mos
→ if relapse = RADS (95% are cured)
 - b) +RFs or unreliable → RADS } PARA-AORTIC (25Gy over ~4wks) vs DOG-LEG RADS
 - need Pelvic CT for para-aortic RADS
→ recurrence higher than DL Rads
 - 5yr survival is ~95% } almost never recurs in abdo
- SURVEILLANCE (moving towards 1st line)
→ single-agent CEMO (carboplatin) } mainly in Europe
- similar results to RADS

What is the recommended surveillance protocol for Stage I Seminomas (EAU guidelines)?

Procedure	Year			
	1	2	3	4-5
Physical examination	3-monthly	3-monthly	Twice/year	Once/year
Tumour markers	3-monthly	3-monthly	Twice/year	Once/year
Chest X-ray	Twice/year	Twice/year	Once/year	Once/year
Abdominopelvic CT scan	Twice/year	Twice/year	Once/year	Once/year

CT = computed tomography scan.

What is the management of STAGE 1S SEMINOMA?

- normal imaging but persistent +ve markers } **RARE SCENARIO FOR SEMINOMA**
- 1) PARA-AORTIC RADS (25Gy over ~4wks) vs FULL DOG-LEG RADS
 - need Pelvic CT for para-aortic RADS } recurrence higher than DL Rads
 - 5yr survival is ~95% } almost never recurs in abdo
 - 2) single-agent CEMO (carboplatin) } **Campbell's says CEMO**
 - similar results to rads but still *investigational*

What is the management of STAGE 2A/B SEMINOMA?

- 1) FULL DOG-LEG retroperitoneal RADS (150cGy/day for total 35-40 Gy)
 - para-aortic, para-caval, bilateral common iliac, ipsilateral external iliac LNs
 - T10-11 down to inguinal incision, lateral to renal hilum
 - if previous herniorrhaphy or prior orchiopexy (potentially altered LN drainage) include contralateral inguinal region (shield contralateral testis)
 - 5yr survival is ~90%
- 2) CHEMO
 - if retroperitoneal disease is close to kidney (3 cycles BEP or 4 cycles of EP)

What is the management of STAGE 2C and 3 SEMINOMA?

- 1) CHEMO
 - GOOD RISK (anyT, anyN, M1a) } 4 cycles EP or 3 cycle BEP \ no RADS because
 - INTERMEDIATE RISK (anyT, anyN, M1b) } 4 cycles BEP / relapse rate is >50%
 - **good risk as long as NO non-pulmonary mets (regardless of primary site, hCG)**
 - better results if no prior rads, but reasonable results for relapse after initial rads
 - extensive prior rads can limit amount of chemo
 - if progression during or recurrence after chemo = SALVAGE CHEMO (VIP)
 - 3-4yr survival rate is ~80-90%

What are the contraindications to retroperitoneal RADS?

- 1) horseshoe kidney (or pelvic kidney)
- 2) renal hilar LNs
- 3) IBD
- 4) prior RADS

What are the complications of para-aortic RADS?

- occurs in 5-10% } less common than with formal Dog-Leg Rads
 - infertility
 - GI complications (radiation enteritis, SBO)
 - 2nd malignancies (~20% at 25yrs)
 - BM suppression

What is the difference between para-aortic RADS only and full Dog-Leg (DL) Rads?

- para-aortic Rads = para-aortic only (usually T10-S1)
- DL Rads = para-aortic, para-caval, bilateral common iliac, ipsilateral external iliac LNs
- same overall and disease free survival } only para-aortic had 4 cases of pelvic recurrences
 - **need pelvic CT surveillance**
- higher rates of S/Es with full DL Rads } diarrhea, leucopenia, infertility, etc

What is the management of POST-CHEMO RESIDUAL MASS FOR SEMINOMA?

- **not common occurrence for seminoma**
- **either fibrosis/necrosis or viable tumour } teratoma very rare**
- 1) diffuse desmoplastic reaction = OBSERVATION } nasty operation
- 2) discrete, well-defined mass with + ve PET scan = resection of mass (nasty)
 - if necrosis/fibrosis = OBSERVATION
 - if viable tumour = SALVAGE CHEMO (vinblastine, ifosfamide, cisplatin)
 - LIMITED ROLE FOR RADS
- 3) discrete, well-defined mass with -ve PET scan
 - a) if <3cm = consider observation
 - b) if >3cm = resection of mass or Bx (RPLND not recommended)
- **viable tumour found in only 10-30% } 80% fibrosis (teratoma extremely rare)**
 - MSK (Herr) → 30% viable tumour if >3cm
 - Brigham and Womens → 20% viable tumour
- poor outcome with salvage chemo
- Jewett } observe for a long time as it can take long time to regress

Non-seminomatous GCT

What is the pattern of presentation of NSGCTs?

- ~**60-70% present with recognizable nodal disease** } **unlike seminoma (75% testis only)**
- chorio often presents with haematogenous mets + small primary tumours in the testis
- **10-15% present with normal markers**

What are the RFs associated with spread of NSGCTs outside the testis?

- 1) **presence of LVI (best predictor)**
- 2) **>40-50% embryonal**
- 3) **proliferation rate >70%**
- 4) **persistently elevated markers (stage 1s)**
- 5) **absence of yolk sac**
- 6) **≥pT2 disease (eg into spermatic cord)**

List contraindications to observation for Stage 1 NSGCTs

- presence of LVI
- embryonal predominance (>40-50%)
- Stage 1s
- ≥pT2
- non-compliance or unable to have close f/u

What is the management of STAGE IA/B for NSGCTs?

- 1) no RFs and reliable → SURVEILLANCE (maybe even for +RFs)
 - 70% don't need RPLND
 - **~30% RELAPSE RATE (cf to 15-20% for seminoma)**
 - **peak at 6 months**
 - 5-10% relapse outside retroperitoneum
 - relapse usually within 2yrs (case reports of 6 and 9yrs – Jewett 5yrs)
 - if relapse = CHEMO is 1st line (RPLND – less common)
 - 3 cycles BEP
- 2) + RFs or unreliable → SURVEILLANCE (moving towards being 1st line)
 - RPLND (1st line, especially if LVI +ve)
 - **25-30% have +ve mets (understaged by imaging)**
 - 90-95% cure rate after RPLND
 - if No → OBSERVATION
 - 5-10% relapse after –ve RPLND
 - high cure rate with chemo
 - lung most common site
 - if N1 (<2cm) → OBSERVATION vs CHEMO
 - ~15% relapse
 - if N2 (>2cm) → CHEMO
 - ~50% relapse rate without Rx
 - 2 cycles BEP
 - if N3 (>5cm) → CHEMO
 - 3 cycles BEP or 4 cycles EP
 - CHEMO
 - 2cycles BEP (NCCN, EAU) vs 3cycles BEP (Campbell's)
 - ~3% relapse rate
 - less invasive, treats mets & requires less intensive f/u cf surveillance
 - 5yr survival rates >95%
 - RADS (uncommon option)
 - more common in EUROPE → doesn't give staging info
 - 40-45 Gy in 4-5wks (para-aortic + ipsilateral pelvic)
 - 15-20% relapse but usually not in retroperitoneum
 - criticized as ineffective } likely this is d.t. understaging
 - may make future Rx difficult → CHEMO for relapses

*** **Dr Jewett/PMH** } **non-risk adapted surveillance for all Stage 1 NSGCTs** ***

What are the advantages of primary RPLND and SURVEILLANCE for Stage IA/B NSGCT?

→ primary RPLND

- staging information
- curative in most with low-volume N1
(25% have RPLN mets → understaged)
- less chance of infertility cf surveillance
+ later Rx (3 cycles chemo)
- avoids persistence of teratoma
- no risk of 2nd malignancies
- less anxiety

→ Surveillance

- no morbidity of surgery } avoid RPLND in ~75% (**only 25% understaged by imaging**)
- maintenance of fertility
- good salvage rates with chemo
- 5-10% relapse outside RP anyway

What is the recommended surveillance protocol for Stage I NSGCTs (EAU guidelines)?

Procedure	Year 1	2	3-5	6-10
Physical examination	3-monthly	3-monthly	Twice/year	Once/year
Tumour markers	3-monthly	3-monthly	Twice/year	Once/year
Chest X-ray	Twice/year	Twice/year		
Abdominopelvic CT scan	Twice/year (at 3 and 12 months)			

CT = computed tomography scan.

What is the management of Stage IS for NSGCTs?

→ normal imaging but persistent +ve markers

- 1) CHEMO } 3 cycles BEP or 4 cycles EP

What is the management of STAGE IIA/B NSGCTs?

→ if markers negative, have option of RPLND } if markers +ve, CHEMO only

1) RPLND (1st line)

- no benefit in routine suprahilar LN dissection if no palpable mets in this region
- ~40% relapse rate after RPLND
- if N1 (LNs <2cm) = SURVEILLANCE
→ if recurrence = SALVAGE CHEMO (3-4 cycles BEP)
- if N2 (LNs >2cm) = ADJUVANT CHEMO (2 cycles BEP)
- if N3 (LNs >5cm) = ADJUVANT CHEMO (3 cycles BEP)
- 5yr survival rate is ~90%

2) CHEMO

- 3 cycles BEP or 4 cycles EP
- option for large (>3cm) retroperitoneal disease
- 5yr survival similar to RPLND ~90%
→ if relapse = POST-CHEMO RPLND

What are the potential complications of RPLND?

- mortality <1%
- 5-25% morbidity
 - general } bleeding, wound infection, PE, DVT, etc
 - GI } bowel injury, ileus, SBO, pancreatitis, bowel ischemia,
 - lung } pneumonia, pneumonitis
 - vascular injury
 - GU } anejaculation
 - lymphatic } lymphocele, chylous ascites (2-3%)
→ milky, high TG, alkaline pH + chylomicro
 - neurologic damage } SC ischemia from aortic mobilization (ligation of artery of Adamkowitz)
→ now less common given limited role for suprahilar dissection

What methods have been used to decrease risk of anejaculation related to RPLND?

- 1) template RPLND } return of ejaculation in 50-90%
→ R-sided dissections better than L-sided ones (**L nerves are dominant**)
- 2) **nerve-sparing RPLND** } **return of ejaculation in >90%**

What is the role of the “nerve-sparing” RPLND? → **new STANDARD OF CARE (Jewett)**

- highest rate of preserved ejaculation
- **preservation of 3 important sets of nerves**
 - 1) **sympathetic chains**
 - 2) **postganglionic sympathetic fibers**
 - 3) **hypogastric plexus**
- return of ejaculation usually >90%
- margins should never be compromised in an attempt to maintain ejaculation

What are the indications for bilateral RPLND for NSGCTs?

- 1) stage 2 disease } nerve-sparing
- 2) post-chemo mass } nerve-sparing possible but difficult
- 3) no response to post-salvage chemo (desperation) } nerve-sparing almost impossible

What are the borders of dissection for the bilateral standard RPLND?

- up to renal vessels
- out to ureters
- down to bifurcation of common iliacs
- back to anterior spinous ligament & psoas fascia
- posterior caval and aortic nodes accessed by dividing lumbar arteries and veins

What is the management of STAGE IIC and III NSGCTs?

- 1) good risk → CHEMO (3 cycles BEP)
(IIC/IIIA)
 - 90-95% response rate, cure rates ~70%
 - a) resolution of disease
→ **OBSERVATION**
 - recurrence → **SALVAGE CHEMO (VIP)**
 - vinblastine, ifosfamide, cisplatin
 - **HIGH DOSE CHEMO + ABMT**
 - CR → **OBSERVE**
 - no R → **DESPERATION SURGERY**
 - b) residual retroperitoneal mass (normal markers)
→ RPLND vs observation
 - ~**40% necrosis/fibrosis** → **OBSERVE**
 - ~**40% adult teratoma** → **OBSERVE**
 - ~**20% viable tumour** → **SALVAGE CHEMO (VIP)**
 - c) residual distant mets
→ **SURGICAL EXCISION**
 - d) persistent markers
→ **SALVAGE CHEMO (VIP)**
- 2) intermediate & poor-risk → CHEMO (4 cycles BEP as soon as possible, clinical trial for IIIC)
(IIIB/C)
 - can also use high-dose chemo + ABMT
 - cure rates are < 60-70%
 - 20-30% have relapse or don't completely respond
 - 2 cycles BEP + 2 cycles BEP with high-dose cisplatin is no better with more toxic side effects (Nichols et al '91)
 - a) residual disease → RPLND
 - b) poor response or + markers → **SALVAGE CHEMO (VIP)**
 - no R → **DESPERATION SX**

*** Campbell's puts “intermediate” into good-risk but NCCN/EAU puts into poor-risk ***

What is the significance of rising markers in the early phase after initiation of CHEMO?

- early rise (first 1-2wks) in markers after starting CHEMO is likely due to tumour lysis syndrome not progression

What is the International Germ Cell Consensus Prognostic Classification System for Testis Cancer?

- 1) Good Risk }} good prognosis + intermediate prognosis
→ goal is to maintain high cure rates BUT decrease toxicity
- 2) Poor Risk }} poor prognosis (no poor prognosis for seminomas)
→ goal is to improve proportion of patients achieving complete response WHILE achieving tolerable treatment side effects

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Good markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any HCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Intermediate markers- any of: AFP 1,000-10,000 ng/mL hCG 5,000-50,000 iu/L LDH 1.5-10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any HCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Poor markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol. 15(2);1997:594-603. Reprinted with permission of the American Society of Clinical Oncology.

What is the management of POST-CHEMO RESIDUAL MASS FOR NSGCTs?

- 1) if elevated markers = SALVAGE CHEMO
→ **RPLND contraindicated if markers +ve**
- 2) if residual mass + N markers post-chemo = RPLND vs observation
→ if >90% shrinkage + no teratoma in testis + <1.5cm = consider OBSERVATION
→ likely NO viable tumour or teratoma (Debono et al '97 - Indiana)
→ if no significant decrease in volume or teratoma in testis or >1.5cm = RPLND
 - evaluates response to chemo, removes viable tumour, directs need for future Rx
 - has high complication rate } ~18% have complications
→ if residual viable tumour (~20%) = consolidation CHEMO
→ MSK (Shinefeld) } if any hx of retroperitoneal disease = RPLND
→ Jewett } any residual mass >1cm = RPLND
- 3) if residual mass post-SALVAGE CHEMO (+/- markers) = DESPERATION Sx

What are some predictors of necrosis in the retroperitoneum post-CHEMO for NSGCTs?

- 30% of predicted necrosis will harbour viable tumour or teratoma
- absence of teratoma in primary
- normal pre-chemo bHCG and AFP
- small pre- or post-chemo mass
- large volume reduction post-chemo

What are the findings on RPLND for NSGCT post-chemo residual mass?

- 40% necrosis/fibrosis → observe (rate of relapse is ~5%)
- 40% teratoma → observe (rate of relapse is ~5%)
- 10-20% viable tumour → consolidation chemo (2 cycles BEP)

What are the prognostic factors for beneficial consolidation CHEMO for viable tumour in post-CHEMO RPLND?

- | | | |
|-----------------------------|---|--|
| 1) incomplete resection | \ | |
| 2) poor-risk classification | } | - beneficial only if 1 RF present |
| 3) >10% viable tumour | / | - no benefit if no RFs present or if ≥ 2 RFs present |

What is growing teratoma syndrome?

- teratoma in retroperitoneum post-chemo for advanced GCTs
- resection of residual teratoma recommended because:
 - growth may compromise vital organ function
 - may see malignant transformation to sarcoma or adenocarcinoma

What are the benefits of completely resecting teratoma, despite its benign nature?

- prevents growing teratoma syndrome
- avoids risk of malignant transformation → 6-8% risk (sarcomas, carcinomas)
- avoids risk of late recurrence of GCT
- prognostic information

What are the high-risk NSGCT post-chemo RPLND groups?

- 1) RPLND post-salvage chemo
 - lower rate of complete resection and higher rate of viable tumour (~50%)
- 2) desperation RPLND
 - elevated markers at time of post-chemo RPLND
- 3) “unresectable” disease
 - 90% experience relapse
- 4) “redo” RPLND post-chemo
 - >50% relapse rate
 - left para-aortic region is most common site of local recurrence post-RPLND

What is the mechanism of action & side effects of CHEMO for GCTs?

- 1) Bleomycin (anti-tumour Abx) → prevents RNA synthesis
→ **pulmonary fibrosis** (1% mortality)
 - destruction of type I and II pneumocytes→ **vascular toxicity**
 - central and peripheral artery disease, Raynaud's
- 2) Etoposide (plant alkylloid) → prevents accurate DNA replication (topoisomerase inhibitor)
aka VP-16 → **myelosuppression**
→ **2° malignancies - leukemia (dose dependent)**
→ alopecia, mucositis
→ mild nephrotoxicity
- 3) cisPlatin (alkylating agent) → directly damages DNA
→ **nephrotoxicity (20-30%) } GFR and salt-wasting**
→ **ototoxicity (30-40% chronic)**
→ **peripheral neuropathy**, Raynaud's, seizures (**hypoMg**)
→ **long-term cardiac toxicity, infertility**
- 4) Vinblastine (vinca plant alkylloid) → anti-microtubule agent
→ **myelosuppression**
→ **peripheral neuropathy**
→ alopecia
- 5) Ifosfamide (alkylating agent) → directly damages DNA
→ **hemorrhagic cystitis } give mesna to prevent it**

Which chemo agents cause significant myelosuppression?

- etoposide
- MTX
- carboplatin
- vinblastine
- thiotepa

What are the predictors of developing pulmonary fibrosis after Bleomycin?

- 1) GFR <80cc/min
- 2) age >40yrs
- 3) advanced disease at presentation
- 4) cumulative dose of bleomycin

*** O2 restriction isn't as important, **BUT fluid management is very important (Donat & Levy '98) *****

What are the contraindications to bleomycin?

- previous bleomycin
- pulmonary disease
- previous pulmonary RADs
- patients unwilling to get bleomycin (high profile athletes)

What is the role of SALVAGE CHEMO for NSGCTs?

- **vinblastine, ifosfamide, cisplatin (VIP) + mesna**
- recurrences post-RPLND followed by surveillance of STAGE IIb
- recurrences post-chemo of STAGE IIb & good-risk STAGE IIc/III } 30% become dz-free
- for viable tumour in RPLND of residual mass post-chemo for good-risk STAGE IIc/III
- for elevated markers post-chemo for good and poor-risk STAGE IIc/III
- NOT for patients that show evidence of progression during BEP

What are the findings on RPLND post-SALVAGE CHEMO for NSGCTs?

- 50% viable tumour
- 40% teratoma
- 10% necrosis/fibrosis

What is 3rd line CHEMO?

→ after failed salvage chemo

- high-dose chemo + ABMT or stem-cell support (carboplatin instead of cisplatin)

What is the risk of second malignancy post CHEMO or RADs?

- ~1.5 times more likely → highest if CHEMO + RADs
- ALL, acute nonlymphoblastic leukemia, melanoma, NHL, colon CA, stomach CA, renal CA, bladder CA, prostate CA, thyroid CA, rectal CA, pancreatic CA, sarcoma

What are the most important prognostic factors in outcomes in testis cancer?

- performance status
- histology
- clinical stage
- pathologic stage
- marker status
- retroperitoneal nodal size

Long Term Issues

What are the long term issues surrounding patients treated for testis cancer?

- 1) fertility
- 2) recurrence of cancer } most common site of late relapse is contralateral testis (2-10%)
→ especially seminoma
- 3) side effects of therapy } 2nd malignancies (20% at 5yrs 2.5x increased risk), HTN, CVD
- 4) anxiety

ALKYLATING AGENTS

Eg cisplatin, carboplatin, cyclophosphamide, ifosfamide, thiotepa, estramustine, nitrogen mustard

Mode of action: directly damages DNA

Toxicities:

Cisplatin → **nephrotoxicity, ototoxicity, peripheral neuropathy**, mild cytopenia, N/V, Raynaud's, gonadal dysfxn

Carboplatin → ototoxicity, nephrotoxicity, hepatitis, hypoMg, hypoK, peripheral neuropathy, **myelosuppression** (worse than cisplatin)

Cyclophosphamide → cytopenia, **hemorrhagic cystitis, cardiomyopathy**, spermatogenic arrest, SIADH

ANTIMETABOLITES }} **“GM-5”**

Eg gemcitabine, MTX, 5-FU

Mode of action: interfere with DNA and RNA division

Toxicities:

MTX → **myelosuppression**, nephrotoxicity, pulmonary fibrosis (minimized by leukovorin), **stomatitis**

Gemcitabine → **nephrotoxic, hepatotoxic**, cytopenia, alopecia

ANTI-TUMOUR ANTIBIOTICS }} **“-mycin's”**

Eg bleomycin, doxorubicin/adriamycin, mitoxantrone, mitomycin C, actinomycin-D

Source: from byproducts of fungus Streptomyces

Mode of action: interfere with enzymes involved in DNA replication, preventing RNA synthesis

Toxicities:

Bleomycin → **pulmonary fibrosis**, pneumonitis, peripheral neuropathy (**NO MYELOSUPPRESSION**)

Doxorubicin/adriamycin → cytopenia, **cardiotoxicity**

Mitoxantrone → **cardiotoxicity**, cytopenia, mucositis

MITOTIC INHIBITORS/PLANT ALKALOIDS }} **“VET”**

Eg Vinca alkaloids (vinblastine, vincristine), etoposide, taxanes (docetaxel)

Source: plant derivatives

Mode of action: antimicrotubule agents

Toxicities:

Docetaxel → cytopenia, redness/soreness of **palms and soles**, peripheral neuropathy, fluid retention

Vinblastine → **neurotoxicity, BM suppression**, glossitis

Vincristine → neurotoxicity, alopecia (**NO MYELOSUPPRESSION**)

Etoposide → mucositis, hepatitis, pneumonia, **BM suppression, secondary malignancies**

What are the pros & cons of each treatment option for NSGCTs, stage for stage?

Stage	Pros	Cons
I		
Surveillance	Avoid morbidity of RPLND Majority (~75%) true stage I (node -) – avoid unnecessary RPLND Survival not impaired if followed closely and salvage RPLND or chemo used promptly 5-10% of relapses outside RP, so need Rx beyond RPLND anyways ? cheaper	~25% radiologically downstaged (nodes truly +) If lost to follow-up or poor compliance, then a problem No definitive surgical staging Mortality in some series ~7%
Primary RPLND	Get definitive staging information 25% radiologically downstaged (cured by RPLND) Chance of subsequent RP recurrence essentially 0 Get definitive surgical staging May save 2 courses of chemo	Morbidity of RPLND Emission failure
Primary XRT	Not used in N.A.	Staging inaccuracy Chemo & RPLND harder post-XRT
Primary chemotherapy	May avoid RPLND High rate of cure No impaired mortality Maintain emission	Morbidity of BEP 75% who are truly node negative receive unnecessary chemo No definitive surgical staging
IIa and IIb Chemotherapy (BEP) +/- salvage RPLND	If nodes completely regress may avoid RPLND Makes RPLND easier Higher chance of nerve sparing if tumour bulk minimized pre-op	Side effects of chemo (2 cycles). Radiologic understaging.
Primary RPLND +/- adjuvant chemo	May avoid 2 cycles of BEP Lower post-op morbidity before belomycin given	May be radiologically understaged (i.e. open and find large masses, more technically difficult) High risk of emission failure if large masses found at time of OR
IIc		
Chemotherapy then RPLND PRN	Makes RPLND easier May avoid RPLND	Side effects of chemotherapy.
Primary RPLND +/- adjuvant chemo	May avoid 2 cycles of BEP.	Large masses technically difficult High risk of emission failure.
III		
Chemotherapy then surgery for residual masses		

EXTRAGONADAL GERM CELL TUMOURS

What is the epidemiology of extragonadal GCTs?

- <1000 reported cases
- **3-5% of GCTs are of extragonadal origin → scrotal U/S to confirm no testicular primary**
- mostly males, except for **female predominance with sacrococcygeal EGCTs**
- most adults present with advanced local disease + distant mets → often without symptoms
- **all germ cell types**
 - pure seminomas account for 50% of mediastinal and retroperitoneal EGCTs
 - sacrococcygeal tumours found in newborns and young adulthood are usually benign
 - sacrococcygeal tumours found in infancy are malignant in 50%
- 2 theories on origin:
 - 1) displacement of primitive germ cells during early embryonic migration from yolk sac endoderm
 - 2) persistence of pluripotent cells in sequestered primitive rests during early somatic development

How do EGCTs differ from testicular GCTs?

- lack encapsulation
- tend to invade or envelope contiguous structures

What are the most common sites of EGCTs?

- 1) **mediastinum (most common)**
- 2) retroperitoneum
- 3) sacrococcygeal region (most benign)
- 4) pineal gland

How do EGCTs present?

- often large with no or few symptoms
- mediastinal → usually in 20's +/- cough, dyspnea, C/P
- retroperitoneal → abdo/back pain, palpable mass, vascular obstruction, constitutional sx's
- sacrococcygeal → neonates, F, palpable mass, skin discoloration, hairy nevus, bowel obstruction, AUR
- pineal → kids, young adults, raised ICP, oculomotor dysfxn, hypopituitarism, hypothalamic

What are the most common sites of spread?

- regional LNs
- lung
- liver
- bone

What are the treatment options for EGCTs?

→ NSGCTs have worse prognosis than seminomas

- mediastinal & retroperitoneal } surgical resection rarely feasible d.t. local extension
 } usually need multi-modal Rx
- sacrococcygeal } wide local excision is Rx of choice as most are benign (except for infants)
- pineal gland } RADs are Rx of choice due to operative morbidity

OTHER TESTICULAR NEOPLASMS

Sex Cord – Stromal Tumours

What is the epidemiology of Sertoli's cell tumour of the testis?

- represents <1% of all testicular tumours
- can occur in any age group } most often patients are <40yrs
- **no strong association with UDT } association with AIS & Peutz-Jeghers**
- 3 main subtypes } classic Sertoli, large cell calcifying form, and sclerosing form (rare)
- grossly, they vary in size from 1-20cm w/ a uniform consistency interrupted by cystic change
- histologically see epithelial elements resembling Sertoli's cells + varying amounts of stroma that is arranged in tubular or solid pattern with vacuolated cytoplasm
 - **may see CALL-EXNER bodies**
 - benign lesions are well circumscribed, malignant ones are less well demarcated
 - invasion of paratesticular structures is suggestive of malignancy
- **10-20% are malignant → evidence of mets is the only reliable criterion of malignancy**
 - malignancy more common if tumour >5cm, +ve LVI & +necrosis
- **feminization (gynecomastia) is usually superimposed with virilization**

What is the management of Sertoli's cell tumours?

- radical inguinal orchiectomy (cures 80-90%)
- imaging to stage } malignant Sertoli's cell tumours can spread to **lung or bone**
- RPLND if evidence of mets
- value of RADs or CHEMO uncertain
- NOW, should consider partial orchiectomy (inguinal approach) if suspicious of Sertoli cell tumour (small intraparenchymal lesion in patient with gynecomastia/virilization), followed by radical orchiectomy if pathology reveals GCT

What is the epidemiology of Leydig's cell tumours of the testis?

- represents 1-3% of all testis tumours } most common sex cord-mesenchymal tumour of testis
- 75% present between 20's and 60's } also common in kids between 3-9yrs of age
- **no association with UDT → cause is likely hormonal based**
- grossly they are small, well circumscribed tumours → usually don't have hemorrhage/necrosis
- histologically see **round, closely packed cells + eccentric nuclei + eosinophilic cytoplasm + lipid vacuoles**
 - characteristic **Reinke's crystals found in 40%**
- **10% are malignant → mets is the only reliable criterion of malignancy** (can't tell on path)
 - malignancy more common in older pts, tumours >5cm, +ve LVI & +necrosis
- in most adults, features of excessive androgen or estrogen may be present
 - eg. gynecomastia, ED, loss of libido, infertility, etc
 - often precedes tumour by 3 or more yrs
- **all kids manifest signs & symptoms of excessive androgen production } need to r/o CAH**
- good prognosis b/c mostly benign → virilizing/feminizing features may take time to resolve
- if malignant, avg survival is ~3yrs

What is the management of Leydig's cell tumours?

- radical inguinal orchiectomy
- endocrine studies } urine estrogens, androgens, corticoids, and pregnanediol may be abN if malignant
- imaging to stage } malignant Leydig's cell mets to **lung, liver, or supradiaphragmatic LNs**
- RPLND an option if histologically/biochemically suspicious for malignant Leydig's cell
- relatively RADs-resistant & CHEMO-resistant
- NOW, should consider partial orchiectomy (inguinal approach) if suspicious of Leydig cell tumour (small intraparenchymal lesion in patient with gynecomastia/virilization), followed by radical orchiectomy if pathology reveals GCT

List pathologic features of Sertoli or Leydig cells that increase likelihood of malignancy.

→ "VANS"

- vascular invasion
- atypia
- necrosis
- size >5cm

What is a Granulosa cell tumour? (EAU Guidelines '08 – Testis Ca)

- rare testicular tumour
- 2 variants } juvenile & adult
 - juvenile type is benign and represents the most common congenital testis tumour (6% of all pre-pubertal testis tumours)
 - cystic appearance
 - adult type presents in mid-40s and has higher chance of malignancy
 - homogeneous with elongated cells and **CALL-EXNER bodies**
- 20% chance of malignancy

Gonadoblastoma

What is the epidemiology of gonadoblastomas in the testis?

- represents <0.5% of testis tumours } **mixed stromal GCT**
- **occurs almost exclusively in patients with gonadal dysgenesis**
 - >25% risk in kids with MGD
- occurs in all age groups but mostly in men <30yrs
- grossly, they vary in size from microscopic to 20cm and may be unilateral or bilateral
 - bilateral in ~40%
 - round, smooth with calcified areas
- on micro, they consist of Sertoli's cell, germ cells, and interstitial tissue ... all in variable proportions ... **CALL-EXNER bodies seen in tubules**
 - ~50% have GCT elements
 - germ cell component prone to malignant degeneration } **most commonly seminoma**
 - if seminomatous elements present referred to as gonadoblastoma + germinoma
- **80% are phenotypically F with primary amenorrhea + lower abdo mass**
 - if phenotypically male, they have UDT + hypospadias + some internal F genitalia
- 90% with gonadal dysgenesis + gonadoblastoma are chromatin -ve and **>50% are XY karyotype**

What is the management of gonadoblastomas?

- radical inguinal orchiectomy
- 40-50% are bilateral so may argue for contralateral gonadectomy when gonadal dysgenesis is present
- excellent prognosis
- if GCT elements present then need to be staged and treated as such
- more commonly found in paed's population (DSD/intersex disorders)
 - undescended testes in mixed gonadal dysgenesis should also be removed
 - gonadal dysgenesis raised as female should have gonads removed
 - scrotal testes can be preserved (lower risk of Ca)

List tumours that may have CALL-EXNER bodies.

- Sertoli cell
- **granulosa cell tumour (original description)**
- gonadoblastoma

Neoplasms of Mesenchymal Origin

What are the mesenchymal neoplasms found in the testis?

- benign fibroma
- neurofibroma
- angioma
- leiomyoma

How do mesenchymal tumours of the testis present?

- painless masses
 - vary in size from small lesions on surface of testis to several centimetres
- Rx → local excision vs radical orchiectomy

What are malignant mesotheliomas?

- malignant tumours developing from **tunica vaginalis**
 - rare, with less than 20 reported cases
 - usually present with associated hydrocele
 - may have local recurrences or even mets to abdomen or lungs
- Rx → radical inguinal orchiectomy
→ RPLND or rads for abdo mets
→ role of chemo uncertain

Miscellaneous Primary Non-GCTs

What are some of the primary non-GCTs of the testis?

- 1) epidermoid cyst → 1% of all testis tumours and most occur in teens to 30's
→ round, firm, well demarcated dense fibrous tissue lined by stratified squamous keratinized epithelium
→ likely a monolayer teratoma } occasionally assoc'd w/ UDT
→ benign but usually managed by radical orchiectomy b/c can't r/o GCT
→ resembles "onion skin" on U/S
- 2) Adenocarcinoma of the Rete Testis → rare but highly malignant tumours
→ occur in adults from 20 to 80yrs of age
→ **multicystic papillary adenocarcinoma**
→ **despite radical orchiectomy, 50% are dead at 1yr**
→ RPLND if only site of spread
→ RADs or CHEMO for mets (lung, liver, bone)
- MTX, fluorouracil, dactinomycin, cyclophosphamide
- 3) Adrenal rest tumours → **bilateral testis tumours associated with CAH**
→ tumours dependent on ACTH so need to Rx CAH not tumours
- 4) Adenomatoid Tumours → benign small tumours usually in epididymis but can occur in testis
→ most common para-testicular mass
- 5) Carcinoid → rare outside GU tract but cases in testis reported
→ usually presents as slow, progressive, painless mass
→ 1° testis carcinoid is cured by inguinal orchiectomy ... if mets, poor prognosis

Secondary Tumours of the Testis

What are the metastatic tumours of the testis?

- 1) lymphoma → accounts for ~5% of testicular tumours
 - **most common 2° neoplasm of the testis**
 - **most common testis tumour in men >50yrs old**
 - diffusely enlarged solid tumour +/- foci of necrosis/hemorrhage
 - diffuse replacement of N architecture with **focal sparing of tubules**
 - all types of lymphoma can present in testis, most are **histiocytic (75%)**
 - usually spreads by hematogenous routes
 - **50% bilateral** (only 10% synchronous)
 - usually presents w/ painless mass but 25% present w/ constitutional symptoms
 - **poor prognosis if;**
 - a) generalized disease found within 1 yr after Dx
 - b) histiocytic type (worse than poorly differentiated lymphocytic)
 - c) bilateral disease
 - d) presenting with lymphoma at other sites
- Rx → CHEMO is treatment for secondary disease
 - orchiectomy if primary
- 2) Leukemic infiltration → **testis is prime initial site of relapse in boys with ALL**
 - most are in relapse at time of testicular presentation
 - Bx is essential to make Dx and orchiectomy is unwarranted
 - infiltration occurs in interstitial spaces +/- destruction of tubules if advanced
 - **bilateral in 50%**
- Rx → testicular RADs (even for unilateral presentation) + CHEMO
 - 2000 cGy in 10 fractions
 - almost all men develop BM relapse
- 3) other metastatic tumours → mets usually involves interstitium and spares tubules
 - mostly an autopsy finding
 - most common primaries are;
 - 1) **prostate (most common)**
 - 2) lung
 - 3) colon Ca
 - 4) melanoma
 - 5) RCC

TUMOURS OF TESTICULAR ADNEXA

What is the incidence of paratesticular tumours?

- **90% are of the spermatic cord**
- 30% malignant } most are mesenchymal sarcomas
 - **rhabdomyosarcoma (most common malignant)**
 - leiomyosarcoma
 - liposarcoma
 - fibrosarcoma
 - myxosarcoma
- 70% benign } **adenomatoid tumour (most common overall)**
 - } lipoma (also common)

Epithelial Tumours

What are the epithelial tumours of the testicular adnexa?

- rare → most testicular adnexal tumours are mesenchymal in origin
- cystadenomas of the epididymis → 1/3 are bilateral and may be associated with VHL
 - most often in young adults
 - similar pathology to RCC

Adenomatoid Tumours

What are the adenomatoid tumours of the testicular adnexa?

- **most common tumour of the paratesticular tissue → 30%**
- found in epididymis, testicular tunicae, and rarely in the spermatic cord
 - most arise in or adjacent to the lower or upper pole of the epididymis (sl. higher)
- usually in 20's or 30's
- small, solid, usually painless masses
- **benign of unknown origin**
- on micro, they have epithelium-like cells and fibrous stroma
- have vacuoles within the epithelial cells
- Rx → surgical excision

What are mesotheliomas of the testicular adnexa?

- more common in older men
- firm, painless mass usually associated with hydrocele
- poorly demarcated lesion with friable areas
- on micro, there's a background of papillary and solid structures against densely fibrous CT
- 15% develop mets in inguinal LNs or abdominal structures
- pure papillary mesotheliomas always prove benign
- Rx → CT chest and abdo
 - radical orchiectomy
 - local Bx if a metastatic focus is suspected
 - RPLND if recurrent disease

Paratesticular Tumours

What is the significance of paratesticular rhabdomyosarcoma?

- occurs mainly in kids & adolescents
- malignant
- **most common malignant paratesticular tumour } accounts for ~40%**
- presents as a large mass that compresses the testis & epididymis
- seems well circumscribed but on micro often extends well beyond the margin
- marked variation on micro from totally undifferentiated mesenchymal elements to distinctive features of skeletal muscle fibers
- **tumour stage & site are the most important prognostic indicators**
- Rx → **radical orchiectomy + RPLND**
 - RADS for local tumours (Cobalt-60 teletherapy)
 - CHEMO (vincristine, cyclophosphamide, dactinomycin)
 - 5yr survival is 75% with multimodal therapy
 - relapses are generally fatal

What is the significance of paratesticular liposarcoma?

- greater frequency than fibrosarcoma, myxochondrosarcoma
- similar to liposarcomas of other soft tissue sites } tend to be well differentiated though
- discrete mass near spermatic cord

What is the significance of paratesticular leiomyosarcoma?

- smooth muscle tumours of the spermatic cord and epididymis are rare
 - malignant
 - hematogenous spread more common than lymphatic spread
 - Electron microscopy used to differentiate the type of sarcoma
- Rx → radical orchiectomy

INFERTILITY AND TESTICULAR CANCER

What are the key points regarding fertility and testicular cancer?

- 1) ~25% present with defects in spermatogenesis (BEFORE any Rx) } >50% have abN S/A
- 2) higher concentrations of anti-sperm Ab's present in men with testis cancer
- 3) ~50% of men are hypofertile after radical orchiectomy
 - stress
 - hormone production by tumour
 - surgical trauma to one testis may effect the other
- 4) 50% of men have normal sperm counts at 2 yrs post-CHEMO } nadirs at ~1yr after chemo
 - majority with N pre-chemo spermatogenesis will return to baseline by 3yrs
 - 25% stay azoospermic
- 5) ~75% paternity post-RPLND vs 35% paternity post-CHEMO
- 6) ICSI makes sperm banking less essential before chemo
- 7) NO increased incidence of birth defects in kids conceived AFTER chemo for testicular Ca
 - avoid pregnancy during chemo as there may be some increased risk
- 8) sperm banking is recommended before chemo

What is the differential diagnosis of gynecomastia?

→ NB. Gynecomastia occurs when T/E ratio altered

- 1) Physiologic
 - Newborn (placental estrogens)
 - Adolescent (plasma estradiol reaches adult level before adult T levels attained)
 - Aging } decreased plasma T concentration
 - } increased conversion of androgen to estrogen
 - } increased plasma T binding globulin and decrease in free T
 - } decreased T:estrogen ratio
- 2) Pathologic
 - deficient T production } congenital anorchia
 - } secondary testicular failure (orchitis, trauma, castration, neurologic & granulomatous disease, renal failure)
 - } Klinefelters
 - } defects in T synthesis
 - deficient T action (AIS, partial AIS)
 - increased estrogen secretion } true hermaphroditism
 - } testicular tumour (Leydig cell, Sertoli cell)
 - } lung carcinoma
 - increased peripheral conversion of estrogen } increased substrate (adrenal dz, liver dz, starvation, thyrotoxicosis)
 - } increased aromatase (obesity)
 - drugs } inhibitors of T synthesis and/or action
 - } anti-androgens → steroidal (cyproterone acetate) or non-steroidal (flutamide)
 - } spironolactone
 - } cimetidine
 - } estrogens (DES, BCP, digitalis, marijuana, heroin)
 - } gonadotropins

Chapter #30 – Surgery of Testicular Tumours

MANAGEMENT OF THE PRIMARY TUMOUR

Radical Orchiectomy

What are the benefits of radical orchiectomy?

- local control of tumour
- provides histopathologic diagnosis
- provides T categorization
- minimal morbidity and no mortality

What are the principles of radical orchiectomy?

- early control of the cord at int. inguinal ring → non-crushing clamp or Penrose tourniquet
- ligate vas and cord vessels separately → silk ligature on cord vessels
- identify and preserve ilioinguinal nerve

What are the possible complications of radical orchiectomy?

- bleeding → scrotal or retroperitoneal
- wound infection
- ilioinguinal nerve injury → parasthesia to medial thigh and hemiscrotum

Scrotal Violation

What are the recommendations for scrotal violation?

- occurs 4-17% of the time → scrotal orchiectomy, trans-scrotal Bx, FNA
- local recurrence rate 3% with scrotal violation (vs 0.4%)
- **no difference in systemic relapse or survival rates } just changes pattern of relapse**
 - 1) low-stage seminoma → extend RADS to include ipsilateral groin and scrotum
 - increased risk of azoospermia
 - 2) low-stage NSGCT → widely excise scrotal scar with spermatic cord remnant at time of RPLND
 - 3) post-chemo patients → should have cord stump removed at time of RPLND
 - extensive groin dissection or hemiscrotectomy is NOT required due to relative absence of local relapse after systemic Rx

Partial Orchiectomy

What are the indications for partial orchiectomy?

- 1) organ-confined, non-palpable polar tumours <2cm and } a) solitary testis
b) bilateral disease
 - 2) suspected benign disease (eg sarcoidosis)
 - still do inguinal approach
- NOT for patients with impaired endocrine fxn pre-op

What are the favorable selection criteria for partial orchiectomy success?

- 1) organ-confined disease with polar mass <2cm
- 2) -ve post-resection Bx of tumour bed (-ve frozen section)
- 3) absence of CIS in remaining parenchyma

What are the principles of partial orchiectomy?

- 1) avoid tumour spillage
- 2) avoid contamination
- 3) cold ischemia (debatable)

Delayed Orchiectomy

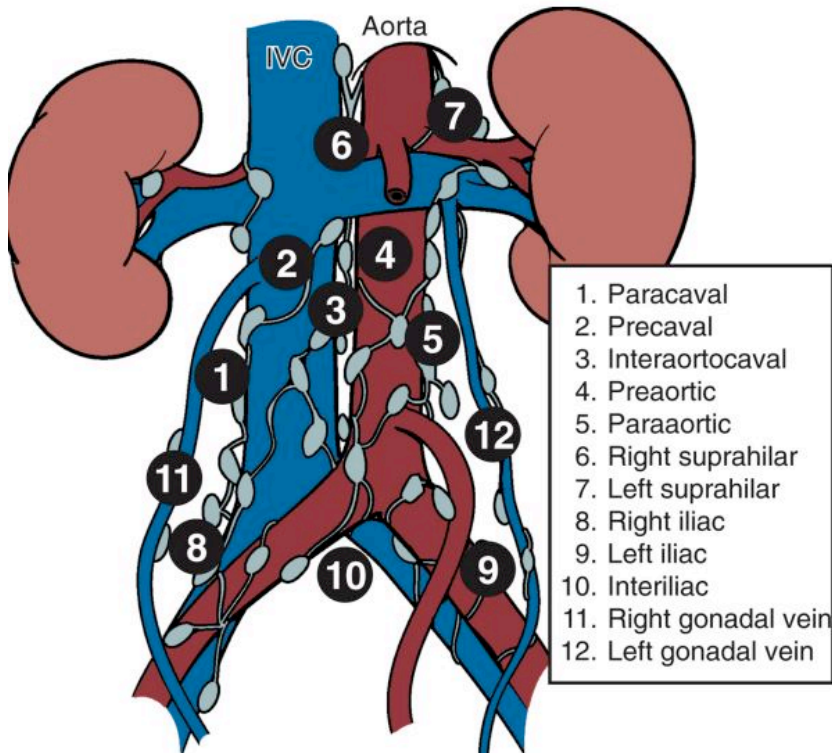
What is the rationale for delayed radical orchiectomy after systemic chemo?

- 25% of patients had viable cancer in testis
- 30% of patients had teratoma in resected testis

STAGING

What is the recommended work-up for testicular cancer?

- 1) History
 - local symptoms } location, onset, duration, pain or painless, radiation of pain, LUTs, STDs
 - metastatic symptoms } neck mass, cough, dyspnea, lumbar back pain, bone pain, leg edema
 - gynecomastia (from increased β hCG)
 - RFs ("His Ca SURFACED") } HIV, Ca in other side, sexual ambiguity, UDT, race, FmHx, age, CIS, maternal estrogen in utero, dysgenetic testes
 - other RFs } recent instrumentation, risky sexual encounters, travel hx, TB exposures, UTIs,
 - PMHx, meds, allergies, EtOH, smoking, drugs
- 2) Physical Exam
 - general appearance, vitals
 - neck & chest exam } supraclavicular LNs
 - abdo exam } masses, DRE
 - genital exam } mass, size, contour, consistency, testicular vs paratesticular, large varicoceles
- 3) lab work
 - tumour markers } AFP, β HCG, LDH
 - CBC, lytes, creatinine, Ca profile, LFTs, PTT, INR
- 4) imaging
 - CXR
 - CT abdo/pelvis } gold standard but not perfect because can't detect micromets
 - MRI is no better than CT for abdomen
 - testicular lesion is hypointense on T2
 - brisk and early enhancement after Gadolinium
 - **good for vascular involvement**
 - CT chest } if CXR is abN, if symptoms suggestive of mets, or +ve retroperitoneal disease on CT
 - **risk of chest disease is <5% if abdo CT is normal**
 - PET scan } often used to evaluate retroperitoneum after chemo (uptake of FDG)
 - like CT, can't detect microscopic nodal disease
 - can't differentiate teratoma from fibrosis } no role for NSGCT post-chemo mass
 - **small role EXCEPT in post-chemo SEMINOMA residual mass**
- 5) miscellaneous
 - discuss sperm banking if suspicious for testis Ca
- 6) surgery } open inguinal radical orchiectomy



THE RETROPERITONEUM AND GERM CELL TUMOURS

Natural Hx, Patterns of Metastasis, Anatomic Considerations

What are the features of GCTs that contributes to successful treatment?

- 1) chemosensitive and radiosensitive ... and also can differentiate to benign teratoma
- 2) rapid growth rate
- 3) frequent production of specific tumour markers
- 4) usually occurs in young, healthy men
- 5) very predictable pattern of spread from retroperitoneum to lungs to posterior mediastinum

What is the lymphatic drainage of the testes?

- R → **inter-aortocaval** then precaval and paracaval LNs
- L → **left para-aortic** and preaortic then inter-aortocaval LNs
- contralateral spread common with right-sided tumours, rare with left-sided tumours, and is usually associated with large-volume disease

What is the rationale behind treating retroperitoneal LNs?

- 1) retroperitoneal nodes are usually the first and often the only site of metastatic spread
- 2) 15-40% of patients are clinically understaged, particularly in the retroperitoneum
 - ~25% have pathological Stage II disease despite clinical stage I diagnosis
 - ~25% retroperitoneal relapse rate in patients on surveillance
 - 20% incidence of teratoma and/or viable tumour in post-chemo RPLND for NSGCT despite NORMAL imaging
- 3) untreated retroperitoneal disease is usually fatal
- 4) most common site of late recurrence of both teratoma and viable GCT is retroperitoneum
 - late recurrences are usually chemorefractory and survival rates are poor

RETROPERITONEAL LYMPH NODE DISSECTION

Evolution of Surgical Templates and Techniques

What is the role of routine suprahilar dissection?

- **NOT done routinely**
- increased morbidity and mortality → increased pancreatic & renovascular complications
- done only if residual disease post-chemo on CT or palpable disease at time of RPLND
→ **most common site of residual suprahilar disease is retrocrural space**

What are the events involved in antegrade ejaculation?

- 1) closure of the bladder neck → **lumbar sympathetics**
- 2) seminal emission → **T12 to L3 sympathetic trunk** forms **hypogastric plexus** just above aortic bifurcation near IMA takeoff
→ hypogastric plexus then forms **pelvic plexus**
→ **R hypogastric nerves are the predominate group to preserve**
- 3) ejaculation → mediated by lumbar and sacral sympathetics
→ **somatic pudendal nerve (S2-S4)** causes relaxation of the EUS and rhythmic contractions of the bulbourethral & perineal muscles

What methods have been used to decrease risk of anejaculation related to RPLND?

- 1) template RPLND } return of ejaculation in 50-90%
- 2) nerve-sparing RPLND } return of ejaculation in >90%

Surgical Technique

What are the basic principles of RPLND?

- 1) understanding of retroperitoneal anatomy and common variations
- 2) excellent exposure
- 3) meticulous “split and roll” technique for lymphadenectomy

What are the advantages of an extraperitoneal thoracoabdominal RPLND?

- 1) easier visualization and dissection of suprahilar LNs
- 2) less risk of post-op SBO
- 3) can perform thoracic procedures simultaneously

Describe the approach to an extraperitoneal thoracoabdominal RPLND.

- lower extremities supine, upper torso in torqued position
- incision from 8th or 9th rib curving downward as a paramedian toward pubic ramus
- subperiosteal rib resection and division of ipsilateral rectus muscle
- peritoneum and contents mobilized and diaphragm divided and pleura entered
- inspect and perform any pulmonary procedures
- expose retroperitoneum to level of contralateral ureter
- RPLND
- chest tube

What are the potential complications specific to the thoracoabdominal RPLND?

- peri-op mortality is ~1.3% and overall rate of complications ~13%
- SBO
- lymphocele
- wound dehiscence
- atelectasis
- prolonged chest tube drainage
- increased need for post-op analgesia

Describe the approach to a transabdominal RPLND.

- incision from sub-xiphisternum to 2cm above pubic symphysis
- divide falciform ligament with silks to avoid capsular tears on liver from retraction
- careful inspection of abdomen, retroperitoneum, and pelvis for resectability
- greater omentum and transverse colon displaced onto chest
- reflect small bowel to right and make posterior peritoneal incision medial to IMV
 - incision carried up to ligament of Treitz and 4th part of duodenum mobilized
 - incision taken down along colonic mesentery through avascular plane between IMV and left gonadal vein
 - IMV may be divided to allow better exposure of left perihilar region
- carry posterior peritoneal incision down to cecum and up right paracolic gutter
- kocherize duodenum to allow mobilization of small bowel, cecum, right colon onto chest
- to minimize traction, divide attachments between the undersurface of duodenum and pancreas and the anterior surface of left renal vein
- always check SMA for pulsations and perfusion of small bowel
- can reflect left colon also to provide better exposure to left parailiac space

What are the important structures to avoid during RPLND?

- 1) SMA and IMA
- 2) pancreas
- 3) renal vessels → ~20% have accessory renal arteries
→ 2-3% will have retroaortic left renal vein (don't confuse as lumbar)
- 4) ureters → vessel loops used to identify and protect the ureters (lateral margin of dissection)

Describe the RPLND.

- dissect out left renal vein and expose anterior surface of aorta
- divide adrenal, gonadal, and lumbar branches with 3-0 silk
- dissect along left renal vein onto anterior surface of IVC
- divide right gonadal vein off IVC
- split and roll lymphatic tissue off IVC and ligate lumbar from IVC
- nerve-sparing technique now employed
 - sympathetic chain runs parallel to great vessels on either side of the spine
→ **L3-L4 are most important nerves to preserve antegrade ejaculation**
 - on L, sympathetic chain is posterior and lateral to lateral border of aorta
 - on R, sympathetic chain is posterior to IVC and postganglionic fibers emerge from medial aspect of IVC
- split and roll lymphatic tissue off anterior surface of aorta down to aortic bifurcation and ligate lumbar from aorta
 - careful of the nerves when performing anterior split, particularly distally
- IMA can be ligated as long as marginal colonic artery is intact
- early division of gonadal arteries prevents hematoma that may result if avulsed
- lymphatic tissue then dissected off psoas fascia & anterior spinous ligament (the posterior limit of dissection)
 - be careful of sympathetic chain when ligating posterior lumbar
- if mets documented or suspected, always perform full bilateral dissection
- IVC, aorta, and renal vessels should be fully skeletonized and the anterior spinous ligament visible, along with the stumps of the gonadal vessels and IMA
- inspect bowel and mesentery for injury
- loosely reapproximate posterior peritoneum with 3-0 silk to prevent direct adherence of small bowel to great vessels

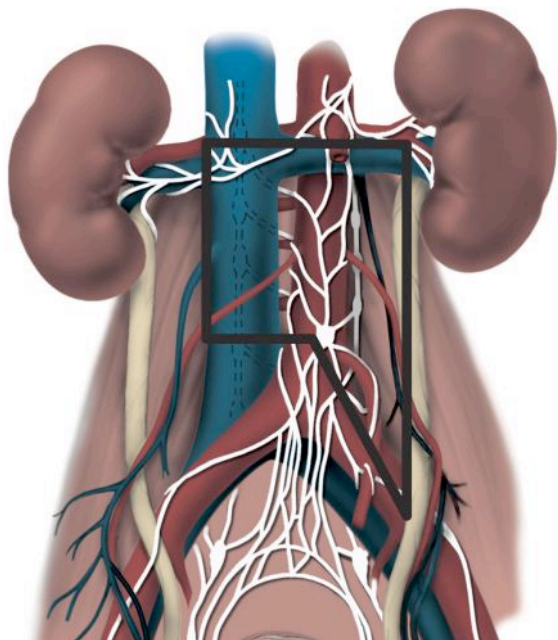
*** post-op tachycardia is common after due to sympathetic discharge ***

What is the role of the “nerve-sparing” RPLND? → new STANDARD OF CARE (Jewett)

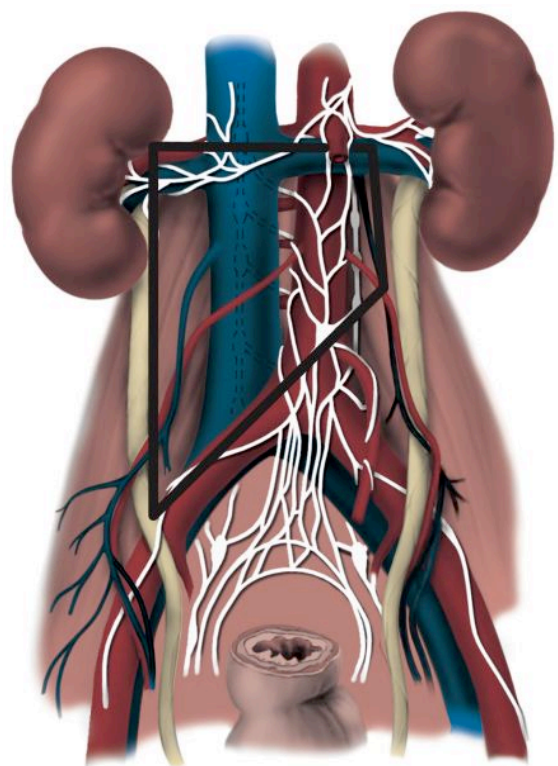
- highest rate of preserved ejaculation
- **sympathetic chains, postganglionic sympathetic fibers, and hypogastric plexus preserved**
- return of ejaculation usually >90%
- margins should never be compromised in an attempt to maintain ejaculation

Which patients are candidates for “nerve-sparing” RPLND?

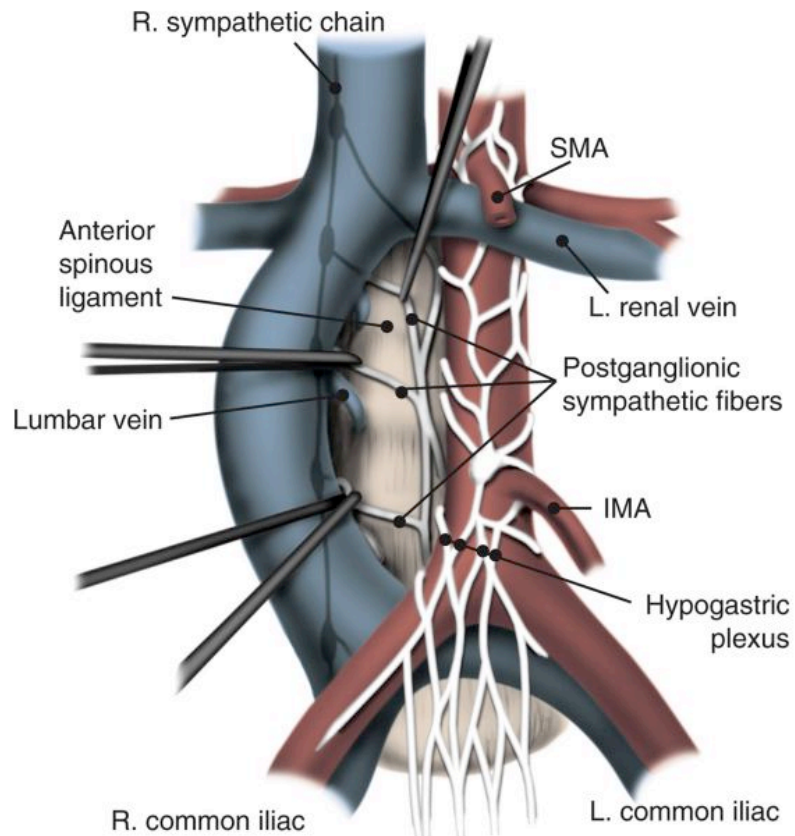
- clinical stage I or low-volume stage II \
- certain post-chemo patients } sympathetic chains, post-ganglionic fibers, and
- becoming STANDARD OF CARE / hypogastric plexus preservation



→ LEFT MODIFIED TEMPLATE

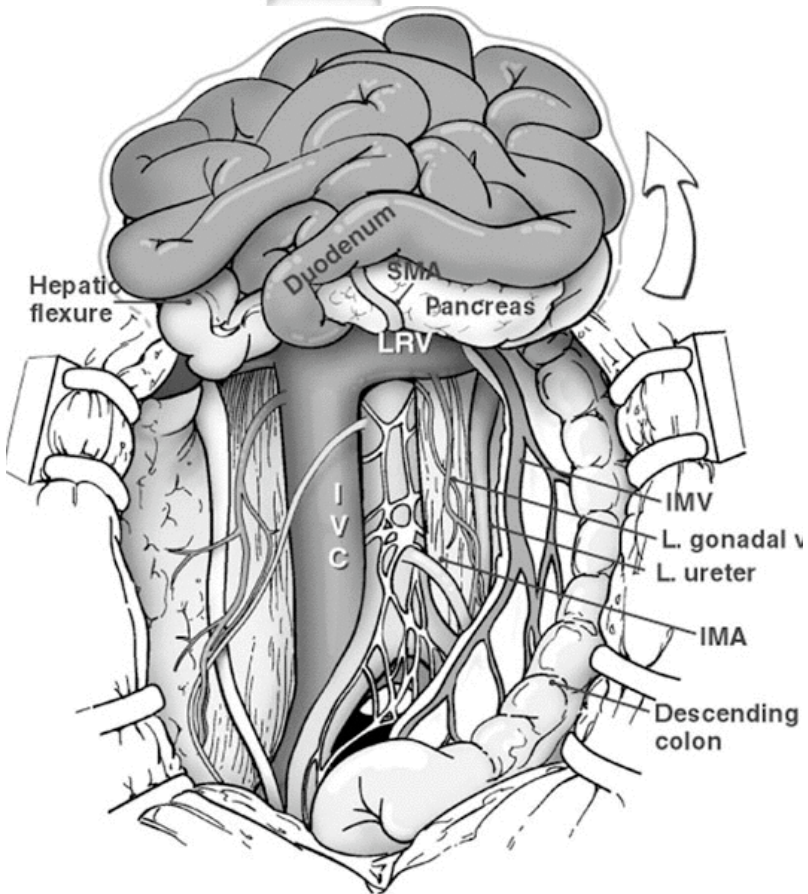
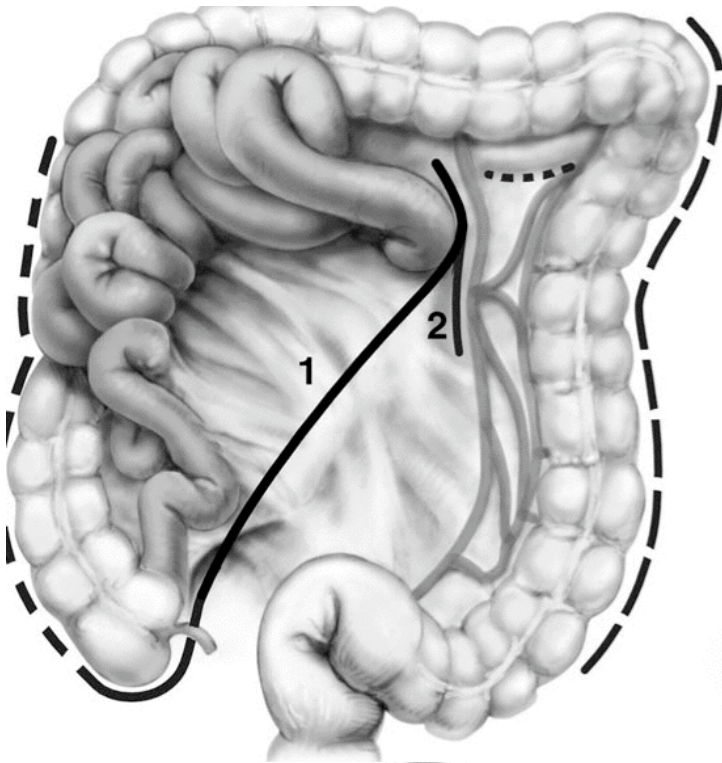


→ RIGHT MODIFIED TEMPLATE



→ MOST IMPORTANT ASPECT IS TO PRESERVE SYMPATHETICS

- 1) SYMPATHETIC CHAINS (bilateral)
- 2) POST-GANGLIONIC SYMPATHETIC NERVES
- 3) HYPOGASTRIC PLEXUS



Laparoscopic RPLND

Describe the L-RPLND.

- position patient in modified lateral position (60 degrees) with elevation of ipsilateral side to be able to change from flank and supine by rotating table
- transperitoneal approach is most common
- camera port via umbilicus + 3 other ports either pararectally or all midline
- R-sided RPLND
 - patient in flank position
 - ascending colon mobilized medially and 2nd portion of duodenum Kocherized to expose entire IVC and renal veins and aorta below level of SMA
 - lymphatic tissue over IVC split medially from renal veins to crossing of ureter
 - be cognizant of accessory renal arteries and insertion of right gonadal vein
 - divide gonadal artery and dissect lymphatic tissue along gonadal vein down to spermatic cord stump in internal ring
 - identify and preserve ureter while vas is clipped and divided medial to external iliacs
 - dissection of right iliacs, paracaval, interaortocaval, and preaortic nodes
 - lymphatic tissue rolled off aorta medially until lumbar
 - if para-aortic nodes going to be removed, lumbar arteries are clipped and transected & dorsal lymphatics split
 - para-aortic lymphatics rolled laterally until fixed to sympathetic chain by lumbar vessels only
 - lumbar vessels clipped to free para-aortic LN package
 - interaortocaval LN package removed by freeing up from medial aspect of IVC and aorta, as well as from posterior spinal attachments
 - make sure good lymphostasis during dissection at cranial aspect
 - paracaval tissue rolled laterally off IVC until it's only attached to sympathetic chain
 - after dissection of postganglionic fibers the paracaval LN package can be removed
 - remove para-aortic, interaortocaval, and paracaval packages
 - replace bowel contents and right colon fixed with one interrupted suture
- L-sided RPLND
 - descending colon mobilized and splenocolic ligament incised
 - tail of pancreas is carefully dissected and swept medially to expose retroperitoneum
 - dissect out left renal vein (cranial border of dissection)
 - clip and transect left gonadal vein
 - divide gonadal artery then dissect lymphatic tissue down along gonadal vein to spermatic cord stump at the internal inguinal ring
 - identify and preserve ureter as it crosses external iliacs
 - dissection of left iliacs, preaortic and para-aortic LNs
 - lymphatic tissue on anterior aspect of aorta split on right side of aorta to level of IMA
 - preaortic LN package rolled laterally down to lumbar arteries (look for accessory LP renal vessels) from renal artery to spermatic cord stump dissection
 - after dorsal split of lymphatic tissue behind aorta the package is rolled laterally
 - be careful when approaching sympathetic chain
 - transect postganglionic fibers and free LN package
 - remove para-aortic and preaortic packages

What are the indications for Lap RPLND?

- 1) clinical Stage I or IIA with negative serum markers
 - 2) absence of comorbidities that preclude safe surgery (eg bleeding diathesis)
 - 3) post-chemo unifocal small-volume residual masses
- *** diagnostic procedure ... may be therapeutic option for low-stage NSGCT ***

What are the indications for bilateral lap RPLND?

- same as for open RPLND → when evidence of mets or suspicious of mets

What are the advantages of lap RPLND?

→ in experienced hands:

- faster recovery
- favourable cosmetic results
- decreased hospital stay
- less post-op pain
- reduced blood loss

What are the disadvantages of lap RPLND?

→ success rates can't be assessed properly

- almost all Stage II patients got post-op chemo
- unclear if lap RPLNDs were performed with therapeutic intent

→ suggested boundaries for lap RPLND are too limited

- on R, no dissection of pre- and para-aortic LNs
- on L, no dissection of interaortocaval LNs

What are the potential complications of lap RPLND?

- chylous ascites → meticulous lymphostasis and pre-op low-fat diet have decreased incidence to <20%
- retrograde ejaculation → 2-5%
- bowel injury → 1-2%
→ colonic, small bowel, duodenum perforation
- vascular injuries
- open conversion rates → 2-5%
→ higher post-chemo

Treatment Options for Low-stage GCTs

What are the treatment options for Stage I NSGCTs?

- 1) RPLND
- 2) surveillance
- 3) chemo (2 cycles BEP)
- 4) RADS (Europe only)

What are the benefits of primary bilateral RPLND for Stage I NSGCTs?

- 1) provides the most accurate N staging
- 2) curative in most patients with Stage I and low-volume N1 disease
- 3) avoids persistence of chemorefractory teratoma in retroperitoneum

What are the benefits of SURVEILLANCE for Stage I NSGCTs?

- 1) avoids morbidity and mortality of RPLND in 75% of patients
 - only 25% of T1NoMo patients with normal markers experience relapse
→ although ~50% of patients with T2-T4 tumours experience relapse
 - retroperitoneum is most common site of relapse
- 2) can still get CHEMO to cure early relapses
 - most relapses occur within first 2 years and are rare after 5 yrs

What factors are predictive of retroperitoneal and/or systemic failure for NSGCTs?

- 1) **LVI (T2)**
- 2) persistently elevated markers
- 3) **>40% embryonal**
- 4) >pT2 disease
- 5) scrotal violation
- 6) absence of yolk sac

What are the drawbacks of CHEMO for Stage I NSGCTs?

- 1) only 5% relapse but exposed to short and long-term effects of chemo
- 2) no long-term f/u data on risk of late relapse from unresected chemoresistant teratoma
 - 20-30% of pathologic Stage II NSGCTs have teratoma in RPLND specimen

What is the management of persistently elevated serum markers post-orchietomy despite negative staging?

- Stage Is
- likely metastatic disease
- CHEMO } 3 cycles BEP or 4 cycles EP

What are the treatment options for Stage II NSGCTs?

- 1) RPLND
 - for Stage IIA or IIB with normal markers
 - post-RPLND observation if pN1
 - adjuvant chemo (2 cycles BEP) if pN2 disease or greater
 - induction chemo (3-4cycles) if incompletely resected or any evidence of residual disease (eg elevated markers)
- 2) CHEMO
 - 3 cycles BEP or 4 cycles EP
 - for Stage IIA or IIB with elevated markers
 - for Stage IIC disease also
 - suprahilar, retrocrural, pelvic, or inguinal LNs
 - contralateral or multifocal LNs
 - back pain
 - salvage chemo if relapse

Surgery for High-stage GCTs

What are the treatment options for Stage IIC and Stage III NSGCTs?

- based on good-risk or poor-risk
- CHEMO → 3 cycles (good) vs 4 cycles (poor)

What are the indications for post-chemo RPLND?

- 1) residual mass with normal markers after primary chemo
 - see below
- 2) residual mass +/- markers post-salvage chemo
- 3) recurrent respectable mass post-salvage chemo
- 4) respectable chemorefractory NSGCT +/- markers

What is the management of POST-CHEMO RESIDUAL MASS FOR NSGCTs?

- 1) if elevated markers = SALVAGE CHEMO
 - **RPLND contraindicated if markers +ve**
- 2) if residual mass + N markers post-chemo = RPLND vs observation
 - if >90% shrinkage + no teratoma in testis + <1.5cm = consider OBSERVATION
 - likely NO viable tumour or teratoma (Debono et al '97 - Indiana)
 - if no significant decrease in volume or teratoma in testis or >1.5cm = RPLND
 - evaluates response to chemo, removes viable tumour, directs need for future Rx
 - has high complication rate } ~18% have complications
 - if residual viable tumour (~20%) = consolidation CHEMO
 - MSK (Shinefeld) } if any hx of retroperitoneal disease = RPLND
 - Jewett } any residual mass >1cm = RPLND
- 3) if residual mass post-SALVAGE CHEMO (+/- markers) = DESPERATION Sx

NSGCTs

Histologic Findings and Management Controversies

What are the findings on RPLND for NSGCT post-chemo residual mass?

- 40% necrosis/fibrosis → observe (rate of relapse is ~5%)
- 40% teratoma → observe (rate of relapse is ~5%)
- 20% viable tumour → adjuvant chemo (VIP)

What are the prognostic factors for beneficial adjuvant chemo for viable tumour in post-chemo RPLND?

- 1) incomplete resection
 - 2) poor-risk classification
 - 3) >10% viable tumour
- beneficial only if 1 risk factor present
→ no benefit if no risk factors present or if 2 or more risk factors present

What are the findings on RPLND post-SALVAGE chemo for NSGCTs?

- 50% viable tumour
- 40% teratoma
- 10% necrosis/fibrosis

Teratoma

What are the benefits of completely resecting teratoma, despite its benign nature?

- prevents growing teratoma syndrome
- avoids risk of malignant transformation → 6-8% risk (sarcomas, carcinomas)
- avoids risk of late recurrence of GCT
- prognostic information

Predicting Necrosis

Which patients are not given RPLND post-chemo?

- “normal” CT and normal markers → LNs <1cm or <1.5cm or <2cm (differing criteria)
→ low attenuation values likely necrosis
- however, there is evidence of residual disease even in “normal” CT patients (~20%)
- PET scan not good at picking out viable tumour in NSGCTs → can’t differentiate necrosis from teratoma

What are some predictors of necrosis in the retroperitoneum post-chemo?

- absence of teratoma in primary
 - normal pre-chemo bHCG and AFP
 - small pre- or post-chemo mass
 - large volume reduction post-chemo
- 30% of predicted necrosis will harbour viable tumour or teratoma

What are the disadvantages of surveillance for “low-risk” post-chemo residual mass?

- viable GCT will progress if unresected and is partially drug-resistant
- cure rate post-salvage chemo is 25% vs RPLND + adjuvant chemo cure rates of 50-70%

Late Relapse

Define late relapse?

- **relapse after a disease-free interval of at least 2 yrs in the absence of a second primary testicular tumour**
- 2-4% rate of late relapse → 60% occur after 10yrs
- most common site is retroperitoneum regardless of initial stage, presentation, treatment etc.
- most late relapses DID NOT have RPLND of residual masses post-chemo
- more common when teratoma is present in a metastatic site
- **late relapses are usually refractory to chemo**

High-risk Post-Chemo NSGCT patients

What are the high-risk NSGCT post-chemo RPLND groups?

- 1) RPLND post-salvage chemo
 - lower rate of complete resection and higher rate of viable tumour (~50%)
- 2) desperation RPLND
 - elevated markers at time of post-chemo RPLND
- 3) “unresectable” disease
 - 90% experience relapse
- 4) “redo” RPLND post-chemo
 - >50% relapse rate
 - left para-aortic region is most common site of local recurrence post-RPLND

Post-chemo RPLND

What are the principles of post-chemo RPLND?

- 1) perform standard bilateral RPLND → some disease will be outside modified templates
- 2) choice of incision depends on location & size → may need thoracoabdominal or costal extension of midline
 - may need “visceral-roll” for large L sides tumours (descending colon, spleen, stomach)

What is the management of residual chest masses post-chemo?

- findings on RPLND may guide the likelihood of finding viable tumour in chest
 - BUT necrosis in RPLND specimen doesn't always predict necrosis in chest
 - **30% have viable tumour or teratoma in the chest despite necrosis in RPLND**
- **ALL thoracic masses post-chemo should be resected**

What are the complication rates for post-chemo RPLND?

- higher than for primary RPLND
- ~20% major complications (vs 8%)
- due to large volume residual disease, post-chemo desmoplastic reaction, bleomycin exposure, more extensive retroperitoneal resection

What is the management of chylous ascites?

- occurs 2-3%
 - diagnosed by paracentesis → **milky coloured, high TG content, alkaline pH, chylomicrons**
 - **RFs include } resected IVC, suprahilar dissection, or simultaneous hepatic resection**
- Rx → diuretics + low-fat diet with medium-chain triglycerides
- somatostatin 100µg tid
 - TPN
 - peritoneovenous shunting for refractory chylous ascites → Leveen or Denver shunts
 - NO re-operation

What is the management of asymptomatic lymphoceles?

- only if causing infection, hydronephrosis, SBO
- needs treatment only 1-2% of the time
- perc drain
- sclerosing agent
- lap marsupialization

What are some other complications of post-chemo RPLND?

→ intraop

- anesthesia-related
- renovascular injury → 2-3% and may need nephrectomy at time of OR
- major vascular injury requiring grafting
- peripheral nerve injury from prolonged positioning eg genitofemoral nerve
- GI injury → duodenum, hepatic, splenic, pancreatic

→ postop

- ileus or SBO
- pulmonary → atelectasis, pneumonia, ARDS
- pancreatitis, pancreatic leak
- bowel infarction
- wound infections, hernia, abscess
- UTIs
- lymphoceles
- chylous ascites
- spinal cord ischemia → <1%
→ with ligation of artery of Adamkowitz

SEMINOMA

What is unique about seminoma and post-chemo residual mass?

- teratoma in the residual mass is very rare
- complete RPLND is often not technically possible due to loss of tissue planes secondary to severe desmoplastic reaction after chemo
→ higher peri-op morbidity than for NSGCT

What is the management of POST-CHEMO RESIDUAL MASS FOR SEMINOMA?

- **not common occurrence for seminoma**
- **either fibrosis/necrosis or viable tumour } teratoma very rare**
- 1) diffuse desmoplastic reaction = OBSERVATION } nasty operation
- 2) discrete, well-defined mass with + ve PET scan = resection of mass (nasty)
 - if necrosis/fibrosis = OBSERVATION
 - if viable tumour = SALVAGE CHEMO (vinblastine, ifosfamide, cisplatin)
→ LIMITED ROLE FOR RADS
- 3) discrete, well-defined mass with -ve PET scan
 - a) if <3cm = consider observation
 - b) if >3cm = resection of mass or Bx (RPLND not recommended)
- **viable tumour found in only 10-30% } 80% fibrosis (teratoma extremely rare)**
 - MSK (Herr) → 30% viable tumour if >3cm
 - Brigham and Womens → 20% viable tumour
- poor outcome with salvage chemo
- Jewett } observe for a long time as it can take long time to regress

FERTILITY IN ADVANCED GCTs

What effects do chemo have on fertility?

- chemo causes Leydig cell AND sertoli cell dysfunction
- spermatogenesis nadirs ~1 yr after chemo
- if pre-chemo S/A was normal, most patients will return to baseline by 3yrs
- overall fertility rates are associated with total dose of platinum delivered
- patient age and pre-chemo FSH levels are also predictive of long-term fertility
- sperm cryo-banking is recommended before chemo
- NO increased incidence of birth defects in kids conceived AFTER chemo for testicular cancer
 - avoid pregnancy during chemo as there may be some increased risk

Chapter #31 – Tumours of the Penis

What is the DDX of a penile lesion?

- 1) benign lesion → noncutaneous
 - congenital and acquired inclusion cysts
 - retention cysts
 - syringomas
 - neurilemmomas
 - benign tumours of supporting structures eg fibromas, lipomas
 - penile pseudotumours eg after ICI
 - phlebitis, lymphangitis, angitis
- cutaneous
 - pearly penile papules
 - hirsute papillomas
 - coronal papillae
 - Zoon's balanitis
- 2) premalignant cutaneous lesions (**"Beware, Pinkus Causes Penile Cancer Later"**)
 - BXO (lichen sclerosis)
 - fibroepithelial polyps of Pinkus } BCC
 - Cutaneous horn
 - Pseudoepitheliomatous micaceous and keratotic balanitis } verrucous
 - Condylomata acuminatum (viral-related)
 - Leukoplakia } verrucous & SCC
- 3) Viral-related lesions
 - Bowenoid papulosis
 - Kaposi's sarcoma
- 4) Verrucous Carcinoma (Buschke-Lowenstein tumour)
 - can degenerate into SCC
- 5) SCC
 - CIS
 - invasive cancer
- 6) Non-squamous malignancies
 - BCC
 - melanoma
 - sarcoma
 - adenosquamous carcinoma
 - lymphoreticular malignancy
 - mets
 - extra-mammary Paget's disease (adenocarcinoma)

List ulcers of the penis.

- malignant } SCC
 - } Kaposi's sarcoma
 - } Buschke-Lowenstein tumour
- infectious } syphilis
 - } chancroid
 - } herpes
 - } lymphogranuloma venereum
 - } granuloma inguinale
- non-specific } Behcet's syndrome
 - } lichen planus
 - } Crohn's disease
 - } trauma
 - } drug reaction

List vesicular lesions of the penis.

- molluscum contagiosum
- pearly penile papules
- herpes
- trauma

List causes of red lesions of the penis.

- SCC
- CIS
- kaposi's
- verrucous carcinoma
- Zoon's balanitis
- cellulitis
- psoriasis
- bowenoid papulosis
- tinea cruris
- fixed drug reaction
- candida
- angiokeratoma
- balanoposthitis

List causes of white lesions of the penis.

- BXO
- leukoplakia
- psoriasis
- lichen planus
- vitiligo

BENIGN LESIONS

Noncutaneous Lesions

What are some benign non-cutaneous lesions of the penile shaft?

- inclusion cysts → congenital (occur in penoscrotal raphe) VS acquired (more common – eg post-Cx)
- retention cysts → from sebaceous glands located on mucosal surface of prepuce or shaft skin
→ may also arise in the parametarial area from obstruction of urethral glands
- syringomas → benign tumours of sweat glands
- neurilemmomas → occur in frenulum & prepuce

What are some benign non-cutaneous lesions of the penile supporting structures?

- neuromas → firm, whitish papules at corona or frenulum
- angiomas → superficial, red macules or papules on corona
- lipomas
- fibromas
- myomas

What are some other benign masses that may mimic carcinoma?

- destructive lipogranulomatous process that develops after injection of oils, implant of FBs, etc
- pyogenic granuloma that develops at injection site of ICI for ED
- atypical Peyronie's plaque
- subcutaneous cords or nodules from phlebitis, lymphangitis, and angitis

Cutaneous Lesions

What are some benign cutaneous lesions of the penis?

- 1) penile papules/hirsute papillomas/coronal papillae
 - normal & common lesions on glans } found in 15% of post-pubertal men
 - } more common in uncirc'd men
 - linear, curved, or irregular rows of conical or globular excrescences } acral **angiofibromas**
 - Rx → observation
- 2) Zoon's balanitis → shiny, erythematous plaque or erosion involving glans or prepuce
 - aka **plasma cell balanitis** } dense plasma cell infiltrate on Bx
 - occurs only in uncircumcised M
 - Rx → Cx



→ PEARLY PENILE PAPULES (benign)



→ ZOON'S BALANITIS (benign)

PREMALIGNANT CUTANEOUS LESIONS

→ BXO, Fibroepithelial lesions of **Pinkus**, **Cutaneous horn**, **Pseudoepitheliomatous Micaceous & Keratotic Balanitis**, **Condylomata acuminatum**, **Leukoplakia**

*** **"Beware, Pinkus Causes Penile Cancer Later"** ***

Balanitis Xerotica Obliterans (Lichen Sclerosis et Atrophicus)

What is BXO?

- **genital lichen sclerosis et atrophicus**
- whitish patch on prepuce or glans → often involves meatus & sometimes fossa navicularis
- glanular erosions, fissures, and meatal stenosis may occur
- occurs most commonly in uncircumcised men → usually middle aged men, sometimes boys
- can cause pain, pruritus, painful erections, and urinary obstruction
- associated with **SQUAMOUS CELL CARCINOMA**
- histology → atrophic dermatitis + **loss of rete pegs** + collagen homogenization on upper 1/3 of skin
→ zone of lymphocytic & histiocytic infiltration

Rx → topical steroid cream (eg Kenaol - triamcinolone), injectable steroids, & surgical excision

→ dilatations or formal meatoplasty for meatal stenosis

→ close f/u and Bx if change in appearance



→ BXO (lichen sclerosis et atrophicus)



→ BXO (lichen sclerosis et atrophicus)

Cutaneous Horn

What is a penile cutaneous horn?

- **lesion that develops over a preexisting skin lesion**
→ wart, nevus, traumatic abrasion, or malignant neoplasm
- overgrowth and cornification of the epithelium, which forms a solid protuberance
- associated with **HPV-16**
- can evolve into a **CARCINOMA** or may develop due to an underlying carcinoma

Rx → surgical excision with a margin of normal tissue + close f/u (can recur after Rx)

Pseudoepitheliomatous Micaceous and Keratotic Balanitis

What is Pseudoepitheliomatous Micaceous and Keratotic Balanitis?

- presents as hyperkeratotic, micaceous growths on glans penis
- may have some microscopic features of **VERRUCOUS CARCINOMA**

Rx → excision, laser ablation, and cryotherapy (reports of fibrosarcoma of glans after Rx)
→ aggressive treatment and close f/u } tends to recur



→ PSEUDOEPITHELIOMATOUS KERATOTIC & MICACEOUS BALANITIS

Leukoplakia

What is leukoplakia of the penis?

- solitary or multiple whitish plaques often involving meatus
- hyperkeratosis + **hypertrophy of rete pegs** + dermal edema + lymphocytic infiltration
- associated with **CIS** and **VERRUCOUS CARCINOMA**

Rx → elimination of chronic irritation, Cx, and Rads + close f/u

VIRUS-RELATED DERMATOLOGIC LESIONS

HPV in Malignant Transformation

What are condylomata acuminata (aka genital warts or venereal warts)?

- **soft, papillomatous growth that can occur as a single lesion or in a moruloid cluster**
- associated with **HPV-6 and HPV-11**
- histology } look for **koilocytes**
- predilection for moist, glabrous areas
- benign and frequently recurs } rare before puberty
- occur most commonly on glans, shaft, and prepuce → **5% have urethral involvement**
→ can go all the way to bladder
- **podophyllin Rx may induce histologic changes suggestive of carcinoma → Bx before Rx**
- associated with **SQUAMOUS CELL CARCINOMA**
- Dx → application of 5% acetic acid causes lesions to turn white (not specific test though)

What are the Rx options for condylomata acuminata?

- 1) medical (for small lesions)
 - topical podophyllin or trichloroacetic acid } historical
 - topical 5% imiquimod cream (Aldara) x 16wks } largely replaced podophyllin
 - 5-FU cream (avoid scrotal skin) x 3wks for intraurethral lesions
 - IFN
 - 2) surgical
 - cryotherapy
 - fulguration and excision
 - laser ablation
 - resection of urethral lesions
- \ /
must use face mask + smoke evacuator to
prevent transference to nasopharynx

What histologic cell type suggests an HPV infection?

- a **koilocyte** → cell with empty cavity around an atypical nucleus

What types of HPV exist?

- >100 subtypes
- types 6, 11, and 42, 43, 44 → associated with gross condylomata and low grade dysplasia
- types **16, 18**, 31, 33, 35, and 39 → **high association with malignant disease**
 - tumour virus transforming proteins E6, E7 may target tumour suppressor gene products (p53, pRB)



→ CONDYLOMA ACUMINATUM

Bowenoid Papulosis

What is Bowenoid Papulosis?

- **presents as multiple papules on penile skin or female vulva**
 - pigmented lesions (2mm to 3cm) → usually on shaft but if on glans, tend to be flat papules
 - associated with **HPV 16** & histologically **resembles SCC CIS** but has a **BENIGN clinical course**
- Rx → observation } spontaneous regression in many patients
→ female partners have **increased risk of cervical Ca** } should get close f/u



→ BOWENOID PAPULOSIS



→ BOWENOID PAPULOSIS

Kaposi's Sarcoma

What is Kaposi's Sarcoma?

- tumour of the reticuloendothelial system
- presents as a cutaneous neovascular lesion → raised, painful, bleeding papule or ulcer
→ bluish discoloration
- found in certain patient populations → AIDS
→ eastern European Jews, Italians, Africans
- due to AIDS epidemic, now the second most common penile malignancy after SCC

What are the 4 subcategories of Kaposi's sarcoma?

- 1) classic → in patients without immunodeficiency } indolent and rarely fatal
- 2) immunosuppressive Rx-related → can reverse with dosage modification of drugs
- 3) African → young men and may be indolent or aggressive
- 4) **epidemic (or HIV-related)** → occurs in AIDS patients (7000-fold increase in likelihood)
→ **strong relationship with HHV-8**

What is the treatment of Kaposi's sarcoma?

- classic & immunosuppressive → rarely associated with diffuse organ involvement
→ treat aggressively if limited to penis
→ modify immunosuppressive agents
→ local excision, partial penectomy, or small-field RADs
→ IFN or chemo for multi-system involvement
- epidemic (HIV-related) → usually not isolated to penis so palliation is goal
→ PU for obstruction, partial or total penectomy, Rads



→ KAPOSI'S SARCOMA

BUSCHKE-LOWENSTEIN TUMOUR

What is a Buschke-Lowenstein tumour of the penis?

- aka giant condyloma acuminatum } form of verrucous carcinoma
 - locally invasive lesion → causes urethral erosion, fistulization, bleeding, etc
 - **does not metastasize**
 - displaces, invades, and destroys adjacent structures by compression
 - no signs of malignant change on histological exam
 - may be related to **HPV-6 & 11 (same as condylomata acuminatum)** } BUT NOT HPV 16 & 18
 - LN mets is very rare → likely represents malignant change of primary lesion
 - mets does occur in other non-penile verrucous carcinomas eg vulva, larynx
 - **recurrence is common & may degenerate into SCC**
- Rx → excision, cryotherapy, systemic IFN + YAG laser ablation
- **NO RADS** } **associated with rapid malignant changes**
 - topical therapy not effective
 - close f/u



→ BUSCHKE-LOWENSTEIN

SQUAMOUS CELL CARCINOMA

Carcinoma In Situ

What is the difference between erythroplasia of Queyrat and Bowen's disease?

- **erythroplasia of Q → CIS of glans or prepuce**
 - **red, velvety**, well-marginated lesion
 - atypical hyperplastic cells w/ hyperchromatic nuclei and mitotic figures
 - capillary proliferation with lots of plasma cells
 - HPV is likely involved (8, **16**, 39, 51)
- **Bowen's → CIS of penile shaft, scrotum or perineum**
 - similar in histology to erythroplasia of Queyrat

What are the RFs for SCC in situ?

- HPV
- ionizing radiation
- immunosuppression
- thermal injury
- arsenic exposure
- chronic dermatoses
- BXO

Does CIS of the penis warrant an internal exam for internal malignancies?

- NO } no association

How often does CIS turn invasive?

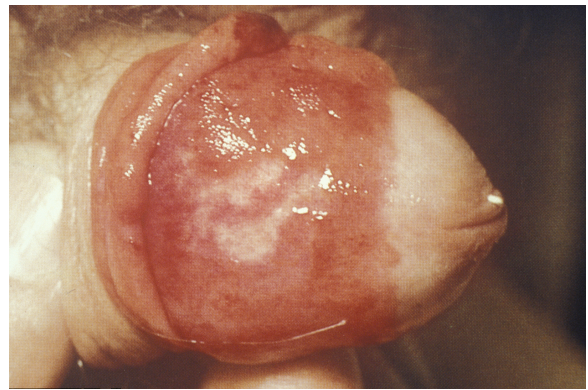
- 10%
- mets very rare

What is the treatment of penile CIS?

- 1) Cx or local excision (5mm margin)
- 2) topical 5-FU (**best 1st line option**)
- 3) YAG (or KTP, CO₂) laser ablation
- 4) RADs if topical-resistant or not candidate for sx
- 5) liquid nitrogen
- 6) ?imiquimod (aldara)



→ SCC in situ } ERYTHROPLASIA OF QUEYRAT



→ SCC in situ } ERYTH. Of QUEYRAT

Invasive Carcinoma

asdf

What is the epidemiology of penile cancer?

- ~0.5% of all male malignancies } decreasing incidence
 - much more common in Asia, Africa, and South American
 - disease of elderly → but also seen in young (30% are <55yrs old)
 - no difference between blacks & whites → BUT, blacks have worse outcomes
- ~95% of penile cancers are SCC

What are the RFs for penile cancer (SCC)? }}} “Penile Cancer Has BURST”

- **Phimosis**
- **CIS**
- **Hygiene (poor)**
- **Beware Causes Penile Ca Later** } BXO, Cutaneous horn, PMKB, Condyloma acuminatum, Leukoplakia
- **UnCx'd patients** → smegma related? (byproduct of bacterial action on desquamated cells)
→ adult Cx doesn't decrease risk
- **RADs**
- **Smoking, chewing tobacco**
- **Trauma (penile)**



→ SCC of PENIS

What is involved in the work-up of a patient with a penile mass?

- 1) Hx
 - assess RF's ("Penile Ca Has BURST") } phimosis, CIS, hygiene, STDs, unCx'd, RADs, smoking, trauma, etc
 - describe lesion and related symptoms
 - size, location, ulceration, bleeding, pain, urethral obstruction, etc
 - constitutional symptoms
- 2) P/E
 - abdomen
 - masses, bladder
 - external genitalia
 - size of lesion, location, characteristics
 - evidence of invasion into corpora, urethra, base of penis/scrotum
 - rectal and bimanual
 - r/o perineal body involvement
 - inguinal exam (bilateral)
 - r/o adenopathy
 - evidence of infection/cellulitis
- 3) Investigations

<ul style="list-style-type: none"> - urine R&M, C&S - CBC, lytes, creat - Ca, Mg, PO, albumin, LFTs, ALP - PTT, INR 	\ } /	most common is anemia, leukocytosis & hyperCa
---	-------------	---
- 4) Biopsy/excision of mass
 - mandatory prior to any Rx
 - may need dorsal slit to reach mass
- 5) Imaging
 - NO IMAGING RECOMMENDED FOR SMALL VOLUME GLANULAR LESIONS
 - if T2 is suspected } U/S or MRI can be helpful if organ-sparing Rx is considered
 - U/S can detect corporal invasion
 - CT not good for penis
 - if palpable nodes or if unreliable P/E → CT abdo/pelvis or MRI
 - CXR → if mets suspected
 - Bone Scan → if mets suspected
 - lymphangiography → NOT RECOMMENDED (unless in study setting)
- 6) Groin dissection
 - for staging
 - superficial dissection or Bx
 - modified complete groin dissection

What are the benefits of circumcision?

- ↓'d risk of penile cancer
- ↓'d risk of HIV (Reynolds et al '04) } GOOD RCTs with significant decrease
- **NO decrease in risk of penile CIS or other STDs**

What is the natural history of penile carcinoma?

- papillary and exophytic OR flat and ulcerative → ulcerative lesions tend to mets to LNs earlier
 - worse 5yr survival
- >5cm or >75% of shaft → tend to mets to nodes faster & have worse survival rate
- penetration of Buck's fascia and tunica albuginea allows invasion into corpora and can lead to vascular dissemination
- ~50% present with lymphadenopathy } of these, 50% have metastatic disease \ ~**35% present w/**
- ~25% with N groins have metastatic disease / **+LN mets**
- mets to inguinal LN's can lead to infection, skin necrosis, sepsis, hemorrhage (erosion into femorals)
- clinically detectable **mets to lung, liver, bone, or brain** are uncommon → 1-10%
- **prolonged loco-regional phase before distant dissemination**
- **death in ~2yrs if not treated**
- second primary neoplasm found in ~15%

Where do the penile lesions first present?

- 1) **glans → 48%**
- 2) prepuce → 21% (only rarely high grade)
- 3) glans and prepuce → 9%
- 4) coronal sulcus → 6%
- 5) shaft → <2% (**usually high grade**)

What is important on physical exam?

- examine and assess **size of lesion**
- r/o involvement of **base of penis and scrotum**
- **rectal and bimanual** to r/o involvement of perineal body
- **inguinal exam for nodes**

What information is necessary from a biopsy?

- confirmation of Dx
- depth of invasion
- presence of vascular invasion
- histologic grade

What are the histologic types of penile SCC?

- **usual type → 60%**
- papillary → 15%
- basaloid → 10% } associated with HPV and demonstrates aggressive behaviour
- warty → 10%
- verrucous → 3% } good prognosis
- sarcomatoid → 3% } demonstrates aggressive behaviour

What is the grading system of penile carcinoma?

- **Broders' classification**
- low, intermediate, high } **50-75% are low grade on presentation**
 - } shaft lesions are more likely to be high grade

What on histology differentiates a low grade lesion from a high grade penile SCC?

- keratin \
- prominent intercellular bridges } **absent in high grade lesions**
- keratin pearls /

What findings on histology are predictive of LN mets?

- 1) T stage (60% if $\geq T2$)
- 2) high grade (~80% for G3)
- 3) % of poorly differentiated cancer (ie >50%)
- 4) vascular invasion
- 5) histologic subtype } basaloid and sarcomatoid
- 6) p53 accumulation

Why do patients get hypercalcemia and how is it treated?

- PTH-related substances made by tumour and mets → activates osteoclastic activity
- Rx
 - NS hydration
 - diuretics if volume overloaded
 - bisphosphonates
 - calcitonin (for severe hypercalcemia)

What imaging studies are used to evaluate penile carcinoma?

- **physical exam still gold standard (especially for examining inguinal nodes)**
- U/S and MRI also can help define penile lesion → MRI adds info if P/E is equivocal
- CT may help for groins if pt is obese or has had previous inguinal surgery → pelvic LNs too

What are the most common sites for distant mets?

- lung
- bone
- liver

What is Jackson's classification of carcinoma of the penis?

- original staging system
- Stage A → confined to glans, prepuce, or both
- Stage B → tumour on shaft
- Stage C → operable inguinal mets
- Stage D → inoperable inguinal mets or involving adjacent structures or distant mets

What is the DDX of penile carcinoma?

- condyloma acuminatum
- Buschke-Lowenstein tumour (verrucous carcinoma)
- BXO
- chancre → painless ulcer from syphilis (*Treponema pallidum*)
- chancroid → painful lesion from GNB (*Haemophilus ducreyi*)
- lymphopathia venereum → painless ulcer from Chlamydia
- granuloma inguinale
- TB

What is the TNM staging system for penile cancer?

- no universally excepted staging system
- TNM still best (AJCC 1997)
- Primary Tumour (T)
 - TX → not assessed
 - T0 → no evidence of tumour
 - Tis → CIS
 - Ta → noninvasive verrucous carcinoma
 - T1 → into subepithelial connective tissue
 - T2 → into corpus cavernosum or spongiosum
 - T3 → into urethra or prostate
 - T4 → into adjacent structures
- Lymph nodes (N)
 - NX → not assessed
 - No → no evidence of tumour
 - N1 → mets to single superficial regional LN
 - N2 → mets in multiple or B/L superficial LNs,
 - N3 → mets to deep inguinal or pelvic LNs
- Distant Mets (M)
 - MX → not assessed
 - Mo → no evidence of tumour
 - M1 → distant mets

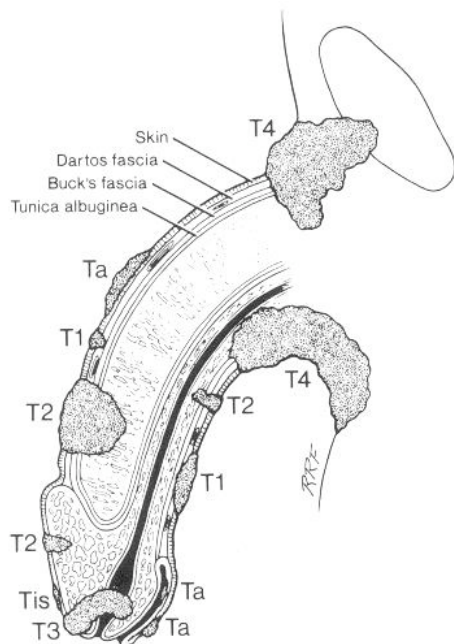
*** **EXTENT OF LN METS IS MOST IMPORTANT PROGNOSTIC FACTOR** ***

Describe the stage groupings for penile cancer

- Stage I → **T₁ NoMo**
- Stage II → **T₂ No-1Mo or T₁N₁ Mo**
- Stage III → **T₃ No-2 Mo or T₁₋₂N₂ Mo**
- Stage IV → **T₄No-3 Mo or T₁₋₄N₃ Mo or T₁₋₄No-3M₁**

What are some of the limitations of the current TNM system for penile carcinoma?

- pathological nodal status requires invasive procedures to accurately determine prognosis
- N2 classification → bilateral or pelvic nodal disease is worse prognosis
- extranodal extension is a dismal prognosis → 5yr survival of 5%
 - not included in staging



What are the investigations required in the work-up of penile cancer?

Table 83–4. MINIMAL DIAGNOSTIC CRITERIA FOR CARCINOMA OF THE PENIS

Primary Tumor (T)

Clinical examination

Incisional-excisional biopsy of lesion and histologic examination for grade, anatomic structure invaded, and presence of vascular invasion

Regional and Juxtaregional Lymph Nodes (N)

Clinical examination

CT scan, if palpable inguinal adenopathy*

Superficial inguinal node dissection (as indicated for high grade, vascular invasion, or invasive histology)

Aspiration cytology (as indicated)

Distant Metastases (M)

Clinical examination

Chest radiograph

Biochemical determinations (liver functions, calcium)

MRI, bone scan (as indicated)

*CT should also be performed in obese patients and in those having prior inguinal surgery, whose physical examinations may be unreliable.

CT, computed tomography; MRI, magnetic resonance imaging.

SURGICAL MANAGEMENT OF THE PRIMARY TUMOUR

Organ preservation

Which patients are suitable for organ-sparing management?

- favorable histology
 - 1) Tis
 - 2) Ta (verrucous)
 - 3) T1 (grade 1 and 2 with no LVI)
- preservation of glans sensation or at least maximize penile shaft length

What organ-sparing therapies exist for low risk penile cancer?

- 1) topical treatments → 5-FU or imiquimod cream (Tis only)
- 2) radiation → brachy, EBRT
- 3) Mohs microsurgery → for CIS or small, distal, superficial tumours
- 4) laser ablation → carbon dioxide, argon, YAG, KTP
 - carbon dioxide not good (only 0.1mm penetration)
 - YAG (penetrates 6mm)
 - comparable recurrence rates to partial penectomy
- 5) limited excision strategies → Cx, limited excision of glans, glans removal w/ shaft sparing
 - need intraop frozen sections
 - 2cm margin needed → **maybe less (esp for small, low grade)**

Penile Amputation

What is the role of partial and total penectomy?

- **still the gold standard for invasive penile carcinoma } 2cm margin likely not essential**
- lower recurrence rates than for organ conserving therapies
- no role for organ conserving therapy for T2 or greater, >3cm, high grade lesions

TREATMENT OF INGUINAL NODES

What is the lymphatic drainage of the penis?

- penile skin
 - originate from ventral surface along median raphe
 - travel laterally around to dorsal aspect of penis } joined here by preputial lymphatics
 - these lymphatics travel SUPERFICIAL to Buck's then divide at base of penis
 - then drainage occurs to superficial inguinal LNs
 - crossover can occur } **nodal involvement can't be predicted based on side of primary tumour**
- glans & corporal bodies
 - lymphatics from glans coalesce at frenulum and merge with lymphatics from distal urethra
 - travel laterally around to dorsal aspect of penis
 - these lymphatics travel DEEP to Buck's along w/ deep dorsal vein } joined by lymphatics of corporal bodies
 - they join with pre-symphyseal lymphatic plexus at base of penis & drain into inguinal LNs
 - **can crossover & can drain directly into deep inguinal LNs**

What is the most important prognostic factor for survival in penile cancer?

→ presence & extent of inguinal mets

- extent of nodal disease is predictive of survival
- argument for early groin dissection

What are the main issues surrounding treatment of inguinal nodes?

- 1) role of prophylactic/adjunctive lymphadenectomy in clinically negative groins
- 2) unilateral vs bilateral lymphadenectomy for unilaterally palpable groin
- 3) should lymphadenectomy be extended to pelvic nodes, unilaterally or bilaterally

Contemporary Indications for Inguinal Lymphadenectomy

What is the prognosis of penile carcinoma patients with resected +ve inguinal nodes?

- NO → 73% 5yr survival
- resected N+ → ~60% 5yr survival } highly dependant on extent of nodal mets
 - 75% if 2 nodes or less
 - 25% if >2 nodes
 - **5% if extranodal extension**
- +ve pelvic nodes → 15% 5yr survival

What factors predict long term survival after inguinal lymphadenectomy (80% 5yr survival)?

- 1) minimal nodal disease (≤2 nodes)
- 2) unilateral involvement
- 3) no extranodal extension
- 4) absence of pelvic nodal mets

How often are palpable inguinal nodes proven to be malignancy?

- **~50% of palpable LNs are cancer**
 - other half is inflammation
- adenopathy after penectomy + 4-6 weeks of Abx is usually mets
 - ~70% incidence of malignancy if still present after 6 weeks of Abx
- late development of nodes is usually mets too

Evolving Indications for Lymphadenectomy in Patients Without Palpable Adenopathy

What are the complications associated with inguinal lymphadenectomy?

- | | |
|--|---|
| <ul style="list-style-type: none">- phlebitis- wound infection → 15%- flap necrosis → 50%- lymphedema of lower limb or scrotum → 50%- seroma → 15%- DVT/PE- femoral vessel or nerve injury | <div style="font-size: 3em; vertical-align: middle; padding: 0 10px;">}</div> <div><p>no complications in only 20%</p><p>→ can be reduced with bedrest,
foot of bed up, compression
stockings, anticoagulants</p></div> |
|--|---|

What changes in pre- & post-op care have decreased complications after groin dissection?

- advances in surgical technique
- plastics consult for myocutaneous flap
- preservation of dermis, Scarpa's fascia, and saphenous vein
- modification of extent of dissection

What is the usual cause of mortality after groin dissection?

- sepsis } usually after concomitant penectomy + groin dissection or after palliative groin dissection

What are the causes of a false-negative groin exam?

- **25-30% false -ve groin exam** } ie 70-75% of all pts with N groins will be No after groin dissection
- obesity
- preexisting edema
- changes from prior therapy (rads, inguinal surgery)

What is the impact of delayed therapeutic groin dissection on long term survival?

- worse long term survival when compared to prophylactic groin dissection & early therapeutic groin dissection for node suspicious/positive patients → 30-60% 5yr survival vs 60-80%
- **rarely salvages patients who experience delayed recurrence**

Contemporary Indications for Expectant Management

Which patients with clinically negative inguinal nodes can follow a watchful waiting protocol?

- low-risk group } <10% incidence of positive inguinal nodes
 - Tis
 - Ta
 - T1 (grade 1 and 2)
 - no vascular invasion

Which patients should be recommended adjunctive groin dissection?

- **high-risk group** } 50-70% incidence of positive inguinal mets
 - ≥T2
 - grade 3
 - vascular invasion
- **palpable inguinal adenopathy**
- **non-compliant patients**

Indications for Modified and Traditional Inguinal Procedures

What options are available for adjunctive Rx of clinical No high-risk penile cancer?

- 1) FNA cytology → 20% false-negative rate (poor sensitivity)
→ NOT RECOMMENDED for STAGING
- 2) sentinel LN Bx, extended sentinel LN dissection → high false-negative rate also
(Cabanas et al) → NOT RECOMMENDED for STAGING
- 3) intraoperative LN mapping → methylene blue or gamma probe
→ SHOULD BE IN RESEARCH SETTING
- 4) **superficial dissection** → removal of all nodes superficial to fascia lata
→ complete dissection if positive on intra-op frozen section
- 5) **modified complete dissection** → proposed by Catalona
 - smaller skin incision, limited field of dissection
 - preservation of saphenous vein
 - thicker skin flaps
 - no transposition of sartorius to cover exposed femorals
 - deep nodes in fossa ovalis removed also

What are the goals of groin dissection in N1 penile cancer?

- 1) eradicate all obvious tumour
- 2) provide coverage for exposed vessels
- 3) provide rapid wound healing → primary closure or myocutaneous flap coverage

What is the management of clinical, unilateral N1 disease?

- bilateral groin dissection → ~50% contralateral mets in clinical, unilateral N1 disease
- superficial contralateral dissection only if negative intra-op frozen section

What is the management of delayed, unilateral lymphadenopathy?

- unilateral groin dissection } especially if long period of surveillance
- consider bilateral groin dissection if bulky recurrence → 30% contralateral mets

What are the indications for pelvic lymphadenectomy?

- should be considered for certain patients
- poor prognosis for pelvic LN +ve disease → 15% 5yr survival
- 1) +ve superficial inguinal disease
- 2) N1 disease with –ve pelvic LNs on pre-op studies
- 3) +ve pelvic LNs that respond to neoadjuvant chemo

What are the arguments for & against early groin dissection?

- For
 - corporal involvement increases risk of LN mets
 - high rate of false –ve groin exam (~30%)
 - bad prognosis if LN mets not resected
 - resection of +ve LN mets potentially curable with long term survival
 - 75% 5yr survival if <2nodes
 - benefit of prophylactic groin dissection over late therapeutic groin dissection
 - late groin dissection rarely salvages patient
 - lower complications than groin dissection after palpable nodes
 - prolonged locoregional phase before distant mets
- Against
 - unnecessary groin dissection in ~70% of patients → high morbidity
 - significant morbidity → phlebitis, DVT/PE, wound infection, flap necrosis, lymphedema, etc

What are the absolute indications for a standard inguinal LN dissection for penile Ca?

- 1) palpable adenopathy after 6wks of Abx
- 2) development of adenopathy after period of surveillance
- 3) +ve sentinel node
- 4) +ve superficial LN dissection

What types of flaps are used for groin coverage?

- 1) **TFL** musculocutaneous transfer
- 2) **rectus abdominis** muscle flap
- 3) **vastus lateralis** muscle flap
- 4) **omental** flaps
- 5) **gracilis** musculocutaneous
- 6) **biceps femoris** musculocutaneous transfer

What is the management of low-risk penile carcinoma?

1) Ti or Ta

- nonpalpable groins → observe
- palpable groins → 4-6 weeks Abx } observe if -ve
 - } FNA cytology if still +ve
 - excisional Bx if -ve
 - if +ve, ipsilateral standard groin dissection
+ contralateral superficial or modified complete dissection

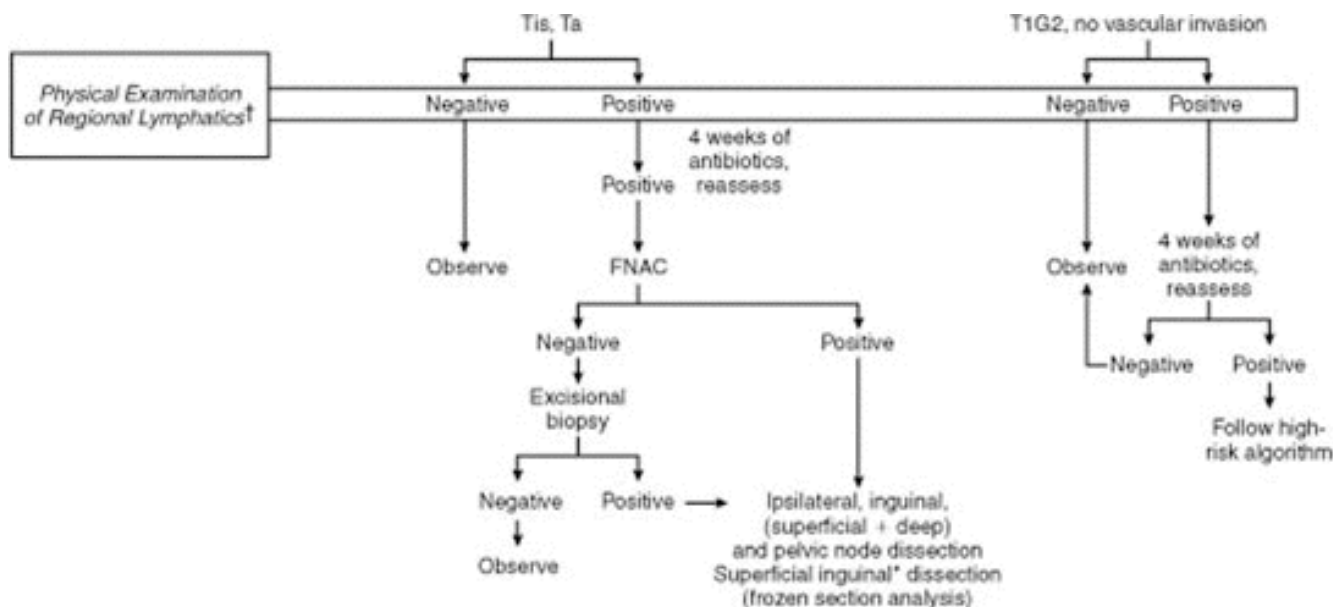
- nonpalpable groins → observe
- palpable groins → 4-6 weeks Abx

} if -ve observe
} if +ve follow high-risk algorithm

➔ for high-risk, ABx have role only to decrease risk of wound infection, NOT to stage nodes

- bilateral nonpalpable groins → bilateral superficial groin dissection (or modified complete)
 - if -ve frozen then observe
 - if +ve frozen, ipsilateral deep + pelvic dissection
- unilateral palpable groin (<4cm) → ipsilateral superficial, deep dissection & pelvic dissection
 - + contralateral superficial dissection (or modified)
 - if -ve, observe
 - if +ve, complete deep + pelvic dissection
- bilateral palpable groins (<4cm) → FNA cytology (??why not do superficial + frozen)
 - if -ve follow bilateral nonpalpable algorithm
 - if +ve do B/L groin and pelvic dissection and consider adjuvant therapy

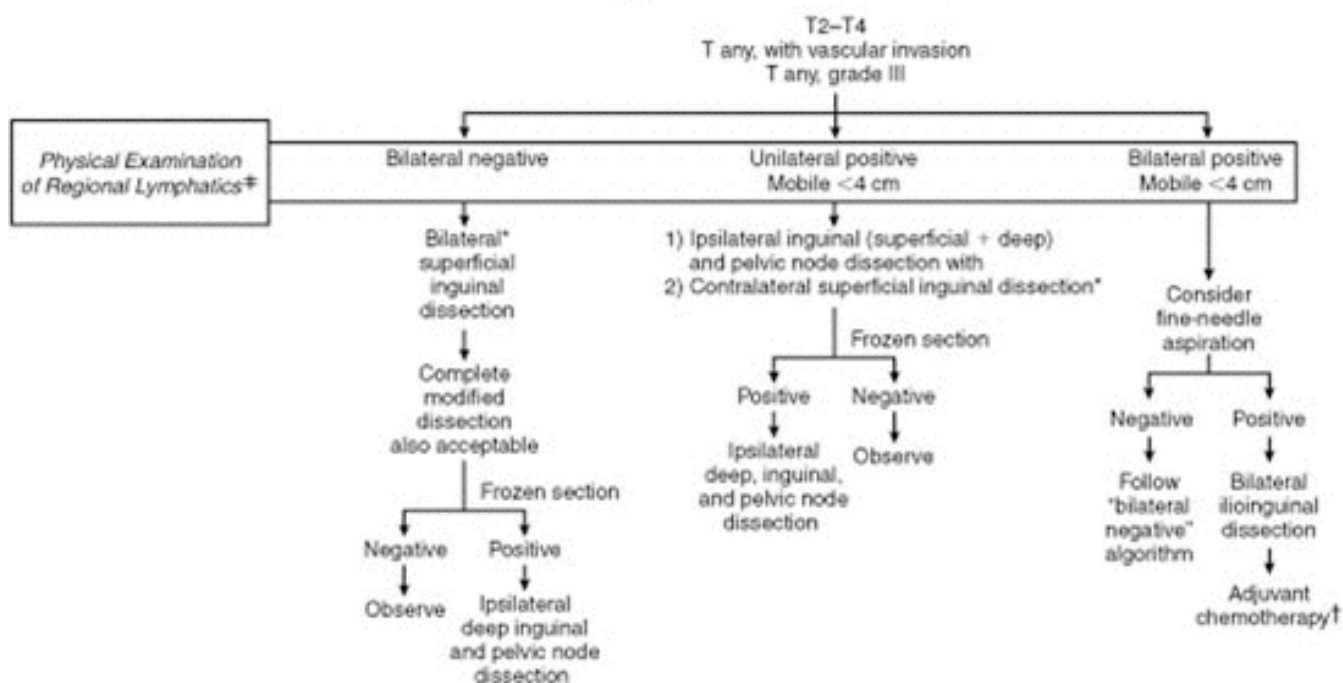
- if response, aggressive surgical resection
- if progressive + resectable, palliative surgery
- if progressive + unresectable, salvage Chemo/Rads or just supportive care



* Complete modified dissection also acceptable.

† Includes physical examination and/or imaging studies.

A



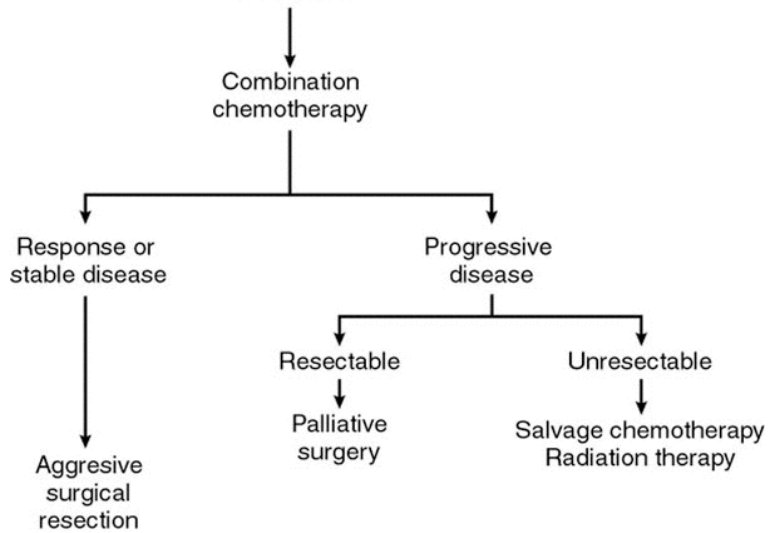
* Complete modified dissection also acceptable.

† Consider if >2 positive lymph nodes extranodal extension of cancer, positive pelvic lymph nodes.

‡ Includes physical examination and/or imaging studies.

B

- 1) Fixed nodal metastases
- 2) >4 cm mobile nodes in inguinal nodes
- 3) Pelvic nodal metastases*



*Subsequent to preoperative imaging studies.

When should you consider adjuvant therapy (CHEMO) for high-risk patients?

- 1) **if >2 nodes +ve**
- 2) **bilateral LN mets**
- 3) **extranodal extension of cancer (worst prognosis)**
- 4) **+ve pelvic nodes**

RADIATION THERAPY

Radiation for the Primary Lesion

What are the indications for EBRT to the primary penile lesion?

→ Cx required first to expose lesion and prevent preputial edema & maceration

- 1) young pt with small (2-4cm), superficial, exophytic, noninvasive lesion on glans or coronal sulcus } 90% response rate
- 2) patients refusing surgical management
- 3) patients with inoperable tumour or distant mets that require local therapy for the primary tumour but want preservation of the penis
- 4) after failed course of 5-FU for CIS

What are the potential side effects of RADs to the penis?

- penile necrosis, edema → 10%
- urethral stricture, stenosis, fistula → 30%
- sensory loss
- ED
- pain

What are the disadvantages of RADs for penile carcinoma?

- SCC is relatively radio-resistant
- high dosages required → concomitant infection will decrease effectiveness
- treatment is usually 3-6 weeks followed by several months of morbidity
- may develop late recurrences
- difficult to distinguish post-RADs ulcer, scar, or fibrosis from possible recurrence
- local failure rate higher than with surgery
- testicular damage

What is the role of brachytherapy for penile carcinoma?

- should be reserved as an option for **low grade, small (<4cm), T1 and T2 lesions**
- acceptable local control rates (80%) with faster dose delivery
- may require salvage penectomy → close f/u required
- late side effects in 50%

Radiation of the Inguinal Areas

What are the arguments against therapeutic RADs to the groins?

- inaccuracy of clinical staging
- lack of histological confirmation of nodal mets
- groins don't tolerate radiation well → skin maceration and ulceration
- concomitant infection will decrease effectiveness of radiation and increase complications
- no benefit in survival vs groin dissection } less effective

What is the role of prophylactic groin RADs for clinical No disease?

→ **NOT RECOMMENDED**

- recurrent groin mets rates are ~20% } similar to incidence of subclinical mets encountered if groin dissection is performed on clinical No groin
- makes clinical evaluation of groin difficult
- increases complication risk if patient needs subsequent groin dissection

What are the indications for groin radiation?

- 1) inoperable fixed and ulcerative groin mets → palliative
- 2) adjuvant therapy after groin dissection for pN+ disease (high-risk)

CHEMOTHERAPY

Active Single Agents and Combination Strategies

What chemotherapy agents have been used for penile carcinoma?

- **cisplatin (DCCP)**
- **bleomycin**
- **methotrexate**
- **vincristine**
- **iv 5-FU**
- paclitaxel
- ifosfamide

What is the role of chemotherapy in penile cancer?

- should be used as part of multimodal strategy (ie consolidated with surgery or rads)
- combination strategies better than single agents
- high toxicity
- usually partial responses and of short duration → cisplatin, MTX, bleo has 50% response rate w/ mean duration of 6 months & median survival of <1 yr

What are the indications for CHEMO in penile cancer?

- primary Rx
 - 1) fixed inguinal nodes
 - 2) ≥4cm nodes
 - 3) +ve pelvic nodes on imaging
- adjuvant Rx after inguinal dissection
 - 1) >2nodes +ve
 - 2) bilateral +ve LN mets
 - 3) extranodal extension
 - 4) +ve pelvic nodes

NON-SQUAMOUS MALIGNANT NEOPLASMS

List malignant lesions of the penis.

- SCC, CIS
- Buschke-Lowenstein (verrucous carcinoma)
- BCC
- melanoma
- sarcoma
- Paget's
- surface adenosquamous carcinoma
- lymphoreticular malignancy
- mets

Basal Cell Carcinoma

What is the treatment of penile BCC?

- rare → <15 reported cases
- **local excision** is virtually curative in all cases
- no reported mets or local recurrences
- **benign variant } pre-malignant fibroepithelioma of Pinkus**

Melanoma

What is the epidemiology of penile melanoma?

- uncommon → <1% of all primary penile malignancies (~150 reported cases)
- presents as blue-black or reddish-brown pigmented papule, plaque, or ulceration on glans
- primary genital melanoma rare } occurs on glans, occasionally on prepuce
- **mets found in ~60% of patients**
- prognosis depends on stage & groin status → good outcomes if low stage & regional LN's are -ve

What is the classification of penile melanoma?

- no formal staging } use of AJCC system for cutaneous melanomas (revised in 2002)
- Stage I → <1mm, no nodes
- Stage II → <4mm, no nodes
- Stage III → regional nodes only
- Stage IV → distant mets

What is the treatment of penile melanoma?

- **Sx is mainstay of Rx** } Stage I – III → partial/total penectomy + bilateral groin & pelvic dissection
- RADs or chemo reserved for adjuvant therapy or palliation

Sarcomas

What is the epidemiology of penile sarcoma?

- rare } “masquerades as Peyronie’s”
- malignant lesions found more proximally, benign lesions often located distally
- presents as subcutaneous mass, penile pain, penile enlargement, urinary obstruction, etc
- **most common malignant lesion is hemangioepithelioma**
- MFH, angiosarcoma, leiomyosarcoma, epithelioid sarcoma, osteosarcoma
- regional mets rare, distant mets more so

What is the classification of penile sarcoma?

- superficial → if arising from integumentary supporting structures
- deep → if from corporal body supporting structures

What is the treatment of penile sarcoma?

- **surgery is mainstay** } superficial → wide local excision and partial penile amputation
 → total penectomy should be considered
- } deep → total penectomy
- recurrences are characteristic of sarcomas
- **groin dissection only recommended if palpable nodes**

Paget's Disease

What is the epidemiology of Paget's disease of the penis?

- rare → <30 reported cases
- presents as erythematous, eczematoid, well-demarcated area that resembles penile CIS
- often get local pain, pruritus, or serosanguinous drainage
- see large, round, clear-staining cells with hypochromatic nuclei (Paget cells)
- **need to r/o periurethral gland adenocarcinoma or sweat gland carcinoma**
- can develop after RADs given for bladder TCC

What is the treatment of penile Paget's disease?

- complete local surgical excision of skin and subcutaneous tissue } local recurrence common
- groin dissection only recommended if palpable nodes } but mets is rare

Adenosquamous Carcinoma

What is the epidemiology of adenosquamous carcinoma of the penis?

- rare
- glandular and squamous histology
- presents as large (4-9cm), firm, greyish-white exophytic mass involving glans or distal shaft

What is the treatment of penile adenosquamous carcinoma?

→ **surgical**

- local excision
- groin dissection only if palpable nodes

Lymphoreticular Malignant Neoplasm

What is the treatment of penile lymphoreticular malignancies?

- rare to be primary
- leukemia may infiltrate penis and cause priapism
- need to r/o systemic disease
- **if primary penile → chemo or local rads**

Metastases

What is the epidemiology of penile mets?

- rare → ~200 reported cases
- **bladder, prostate, rectum** most common primaries → may also see renal and lung neoplasms
- **presents most often as priapism**
- usually appears rapidly after recognition and treatment of the primary
- often represents advanced disease elsewhere so survival after presentation is usually <1 yr

What is the treatment of penile mets?

- look for primary
- penectomy usually reserved for palliation of pain
- rads usually not successful
- most will die within 1yr

ALKYLATING AGENTS

Eg cisplatin, carboplatin, cyclophosphamide, ifosfamide, thiotepa, estramustine, nitrogen mustard

Mode of action: directly damages DNA

Toxicities:

Cisplatin → nephrotoxicity, ototoxicity, **peripheral neuropathy**, mild cytopenia, N/V, Raynaud's, gonadal dysfxn

Carboplatin → ototoxicity, nephrotoxicity, hepatitis, hypoMg, hypoK, peripheral neuropathy, **myelosuppression** (worse than cisplatin)

Cyclophosphamide → cytopenia, **hemorrhagic cystitis**, cardiomyopathy, spermatogenic arrest, SIADH

ANTIMETABOLITES }}} “GM-5”

Eg MTX, gemcitabine, 5-FU

Mode of action: interfere with DNA and RNA division

Toxicities:

MTX → myelosuppression, nephrotoxicity, pulmonary fibrosis (minimized by leukovorin), stomatitis

Gemcitabine → nephrotoxic, hepatotoxic, cytopenia, alopecia

ANTI-TUMOUR ANTIBIOTICS }}} “-mycin's”

Eg bleomycin, doxorubicin/adriamycin, mitoxantrone, mitomycin C, actinomycin-D

Source: from byproducts of fungus Streptomyces

Mode of action: interfere with enzymes involved in DNA replication, preventing RNA synthesis

Toxicities:

Bleomycin → **pulmonary fibrosis**, pneumonitis fevers and chills (**NO MYELOSUPPRESSION**)

Doxorubicin/adriamycin → cytopenia, **cardiotoxicity**

Mitoxantrone → **cardiotoxicity**, cytopenia, mucositis

MITOTIC INHIBITORS/PLANT ALKALOIDS }}} “VET”

Eg vinca alkaloids (vinblastine, vincristine), taxanes (docetaxel), etoposide

Source: plant derivatives

Mode of action: antimicrotubule agents

Toxicities:

Docetaxel → cytopenia, redness/soreness of **palms and soles**, peripheral neuropathy, fluid retention

Vinblastine → neurotoxicity, BM suppression, glossitis

Vincristine → neurotoxicity, alopecia (**NO MYELOSUPPRESSION**)

Etoposide → mucositis, hepatitis, pneumonia, BM suppression, **secondary malignancies**

- 1) CO₂ laser
 - 10,600nm wavelength
 - vaporization to skin depth of 0.01 mm and coagulation of blood vessels up to 0.5 mm
 - used for dysplastic lesions and CIS } local recurrence rate of CIS as high as 33%
 - good cosmesis
- 2) Nd:YAG laser
 - **most commonly used laser for penile SCC**
 - penetrates skin 3-6mm } better cancer control for small superficial SCC
 - } ~20% local recurrence rate for CIS and T1 SCC
- 3) KTP laser
 - 532nm wavelength
 - intermediate depth of penetration relative to CO₂ and Nd:YAG
 - better hemostasis than CO₂ laser

What methods are used to make laser therapy more effective?

- combine with surgical excision } laser of base and margins
- use of acetic acid prior to laser therapy to mark out HPV-induced areas
- use of 5-ALA and autofluorescence to direct biopsies in order to assess margin status

Mohs Micrographic Sx

What are the indications for Mohs surgery for penile cancer?

- | | | |
|---------------------|---|--------------------------|
| 1) CIS | \ | cure rates comparable to |
| 2) small T1 tumours | / | partial penectomy |

What are the advantages & disadvantages of Mohs micrographic surgery for penile cancer?

→ advantages

- excellent local control rates } better with smaller lesions
- maximizes organ preservation

→ disadvantages

- labour intensive
- requires technical expertise

Conservative Surgical Excision

What are the indications for conservative surgical excision of penile cancer?

- 1) distal tumours of preputial skin or glans
- 2) CIS
- 3) small T1 tumours
- 4) manageable T2 tumours in patients refusing more aggressive surgery

What are the different conservative surgical excision strategies used for penile cancer?

- 1) circumcision (for distal preputial tumours)
- 2) local excision
- 3) glansectomy } better than partial penectomy for sexual function
 } if margins +ve then need to perform distal corporectomy

→ intra-op frozen section critical } local recurrence rate is ~10%

What are the advantages & disadvantages of conservative surgical excision for penile cancer?

→ advantages

- good option when laser and Mohs surgery not available
- provides tissue for grading and assessment of margins (unlike laser therapy)
- doesn't require technical expertise (unlike Mohs surgery)

→ disadvantages

- [illegible]

What are the goals of partial penectomy?

- successful local control } 2cm margin (debatable now)

- Describe the main steps of a partial penectomy.

- exclude lesion from surgical field (towel, glove, etc) } some use tourniquet at base of penis

- How successful is partial penectomy?

- ### Total Penectomy

- **penis amputated at or near the level of the suspensory ligaments**

- What are the indications for a total penectomy?

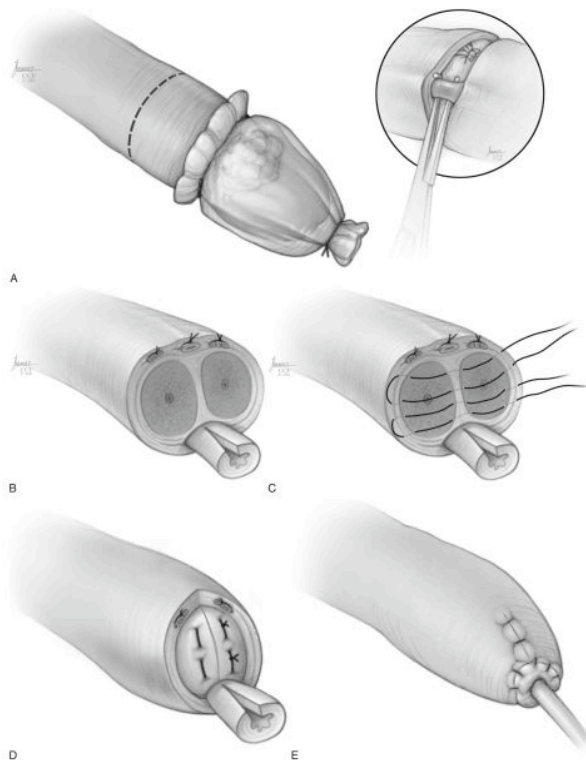
- Describe the main steps of a total penectomy.

- exclude tumour from surgical field
- incise skin and dartos fascia at base of penoscrotal junction
- dissect plane between tunica albuginea and Buck's fascia dorsolaterally
- ligate and divide dorsal vessels
- sharply transect corporal bodies and urethra at same level
- close corpora with interrupted horizontal mattress 2-0 sutures
- mobilize urethra from surrounding bulbospongiosus muscle and dorsally from corporal bodies
- small U-shaped incision made in perineum at site of PU
- transpose mobilized urethra through perineal opening without angulation
 - can also construct a flap inlay urethrostomy without mobilization of the urethra
 - λ incision in perineum + ventral urethrotomy incision made in mid to proximal bulbous urethra
- spatulate urethra dorsally and PU is constructed using interrupted 3-0 sutures
- Penrose drain left in situ
- urethral catheter left in situ for 7-10 days

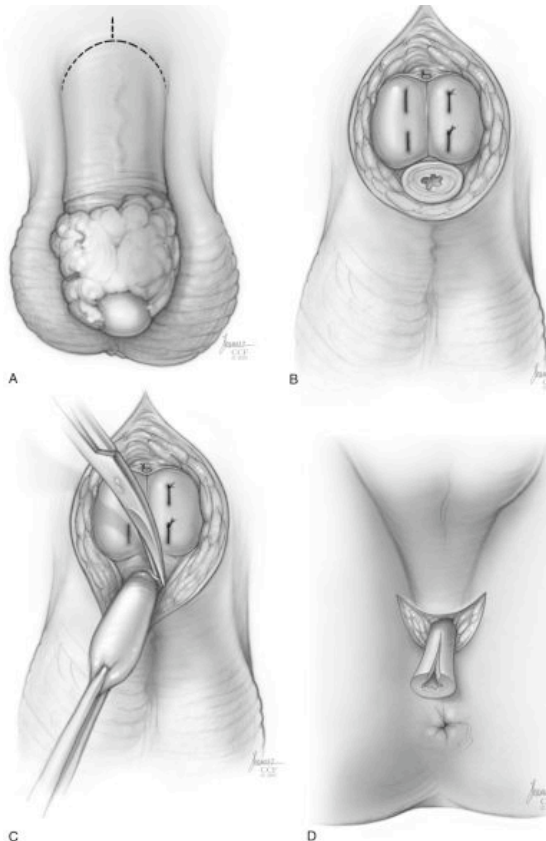
Radical Penectomy

Describe a radical penectomy.

- not commonly done
- patient placed in lithotomy
- incision of skin and dartos at penoscrotal junction as for total penectomy
- mobilize corporal bodies off ischiopubic rami proximally until dorsal vein is seen
- ligate and divide dorsal vein
- modified lambda incision made in perineum
- penis brought out through perineal incision
- dissection of corporal bodies continued to tips of crura
- suture ligatures used to control dorsal penile & cavernosal vessels near dorsal aspect of crura & in the penile hilum
- urethra transected after plane developed between proximal urethra and corpora
 - leave 2-3cm of urethra to form a PU
- standard flap perineal urethrostomy made
- Penrose drain left in situ
- urethra catheter left in situ for 7-10days



→ PARTIAL PENECTOMY



→ TOTAL PENECTOMY



→ PERINEAL URETHROSTOMY

Inguinal Lymph Nodes

What is the lymphatic drainage of the penis?

- **can spread bilaterally to inguinal LNs, but once inguinal, goes to ipsilateral pelvic only**
- prepuce & skin of penile shaft } converge dorsally, travelling superficial to Buck's fascia, then divide at base to drain into L & R superficial inguinal nodes
- glans } toward frenulum then through penis, within Buck's fascia, draining through pre-symphyseal lymphatics into the superficial then deep inguinal LNs
- inguinal nodes } drains to ipsilateral pelvic LNs

What separates the superficial from the deep inguinal LNs?

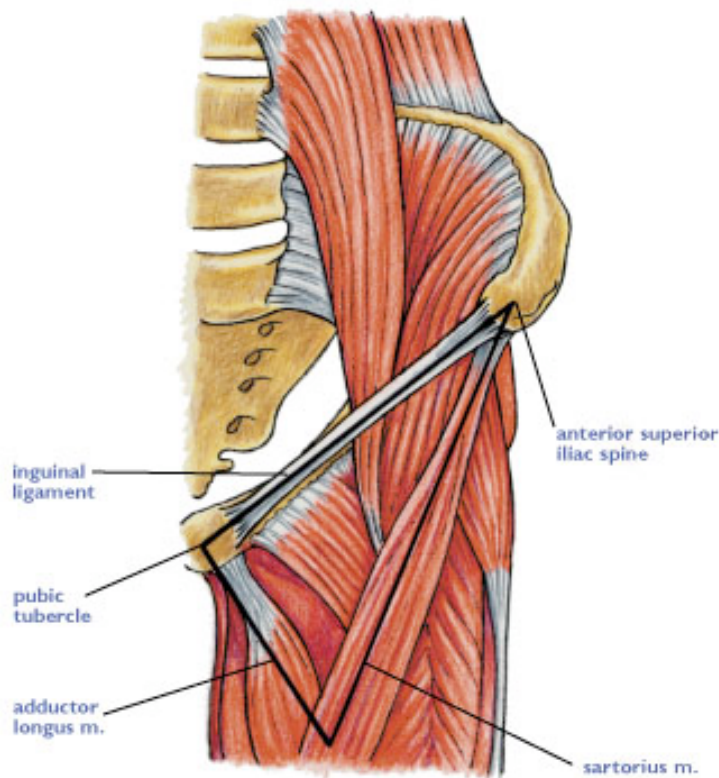
- fascia lata of the thigh
- through femoral triangle

What are the borders of the femoral triangle?

- superiorly } inguinal ligament
- medially } medial border of adductor longus muscle
- laterally } medial border of sartorius muscle
- floor } pectineus muscle medially and iliopsoas laterally
- roof } tensor fascia lata

→ **saphenofemoral junction lies 2 fingerbreadths lateral & inferior to pubic tubercle**

→ contents include femoral artery, vein, nerve, lymphatics, femoral branch of GF nerve



→ FEMORAL TRIANGLE

What are the 5 anatomic groups of the superficial inguinal LNs?

- 4-25 LNs situated in deep membranous layer of superficial fascia of the thigh (Camper's)
 - 1) central nodes (around saphenofemoral junction)
 - 2) superolateral nodes (around superficial circumflex vein)
 - 3) inferolateral nodes (around lateral femoral cutaneous and superficial circumflex veins)
 - 4) superomedial nodes (around superficial external pudendal and superficial epigastric veins)
 - 5) inferomedial nodes (around greater saphenous vein)

Where are the deep inguinal nodes?

- **fewer in number than superficial inguinal**
 - lie primarily medial to femoral vein in femoral canal
 - node of Cloquet is most cephalad of this deep group

Why is the vasculature of the flaps (created after inguinal node dissection) tenuous?

- blood supply to skin of inguinal region derive from **branches of common femoral artery**
 - superficial external pudendal
 - superficial circumflex iliac
 - superficial epigastric
- complete inguinal dissection requires ligation of these branches
- viability of the skin flaps depends on anastomotic vessels in the superficial fatty layer of Camper's fascia that course lateral to medial
- TRANSVERSE SKIN INCISION LEAST COMPROMISES THIS BLOOD SUPPLY

What is the function of the femoral nerve?

- motor } pectineus, quadriceps femoris, sartorius muscles (knee extension)
- sensory } anterior thigh

What is the role of sentinel node biopsy?

- initially reported to have 90% survival if normal (Cabanas)
- **located at saphenofemoral jxn } 2 fingerbreadths lateral & inferior to pubic tubercle, & found superomedial to saphenous vein insertion**
- others have found extensive regional mets to occur with normal sentinel node Bx
- efforts to improve sentinel node Bx include:
 - lymphoscintigraphic imaging (gamma probe) + blue dye (eg indigo carmine)
 - U/S with FNA of any abN-looking nodes
- ➔ **overall disappointing and not done often } research settings**

Risk-based Management of the Inguinal Region

What is the management of low-risk penile carcinoma?

- 1) Tis or Ta
 - nonpalpable groins → observe
 - palpable groins → 4-6 weeks Abx } observe if -ve
 } FNA cytology if +ve
 → excisional Bx if -ve
 → if +ve, ipsilateral groin dissection
 + contralateral superficial or modified complete dissection
- 2) T1, grade 1-2
 - nonpalpable groins → observe
 - palpable groins → 4-6 weeks Abx } if -ve observe
 } if +ve follow high-risk algorithm

What is the management of high-risk penile carcinoma?

➔ for high-risk, ABx have role only to decrease risk of wound infection, NOT to stage nodes

- 1) $\geq T2$, any T with vascular invasion, any T with grade 3
 - bilateral nonpalpable groins \rightarrow bilateral superficial groin dissection (or modified complete)
 - \rightarrow if -ve frozen then observe
 - \rightarrow if +ve frozen, ipsilateral deep + pelvic dissection
 - unilateral palpable groin ($<4\text{cm}$) \rightarrow ipsilateral superficial, deep dissection & pelvic dissection + contralateral superficial dissection (or modified)
 - \rightarrow if -ve, observe
 - \rightarrow if +ve, complete deep + pelvic dissection
 - bilateral palpable groins ($<4\text{cm}$) \rightarrow FNA cytology (??why not do superficial + frozen)
 - \rightarrow if -ve follow bilateral nonpalpable algorithm
 - \rightarrow if +ve do B/L groin and pelvic dissection and consider adjuvant therapy
- 2) fixed groin nodes, $>4\text{cm}$ inguinal nodes, or pelvic nodes \rightarrow CHEMO first
 - \rightarrow if response, aggressive surgical resection
 - \rightarrow if progressive + resectable, palliative surgery
 - \rightarrow if progressive + unresectable, salvage Chemo/Rads or just supportive care

What are the indications for a standard inguinal LN dissection for penile cancer?

→ ABSOLUTE

- 1) palpable adenopathy after 6 weeks of Abx } do modified on other side even if N
- 2) development of +ve LNs after period of surveillance } if long surveillance period,
don't need to do other side
- 3) +ve sentinel node
- 4) +ve superficial node dissection

→ RELATIVE

- 1) impalpable LNs with high-risk penile cancer (high T stage or grade) } eg T1 G3
→ **modified inguinal LN dissection is other option**

What is the role for Catalana's modified inguinal LN dissection?

→ **primary use is in patients with a primary tumour with high-risk for inguinal mets & clinically normal groins on examination**

- excellent assessment of regional nodes
- **if nodal mets detected on frozen-section, modified dissection converted to a standard extended inguinal LN dissection**
- false-negative rate is ~0-5%

What are the benefits of the modified inguinal LN dissection?

→ provides staging info & therapeutic benefit similar to standard extended inguinal LN dissection
WITH LESS MORBIDITY

- 1) shorter skin incision
- 2) limitation of dissection by excluding the area lateral to femoral artery and caudal to fossa ovalis
- 3) preservation of saphenous vein
- 4) elimination of need to transpose sartorius muscle

Describe the main steps of the Catalana modified inguinal LN dissection?

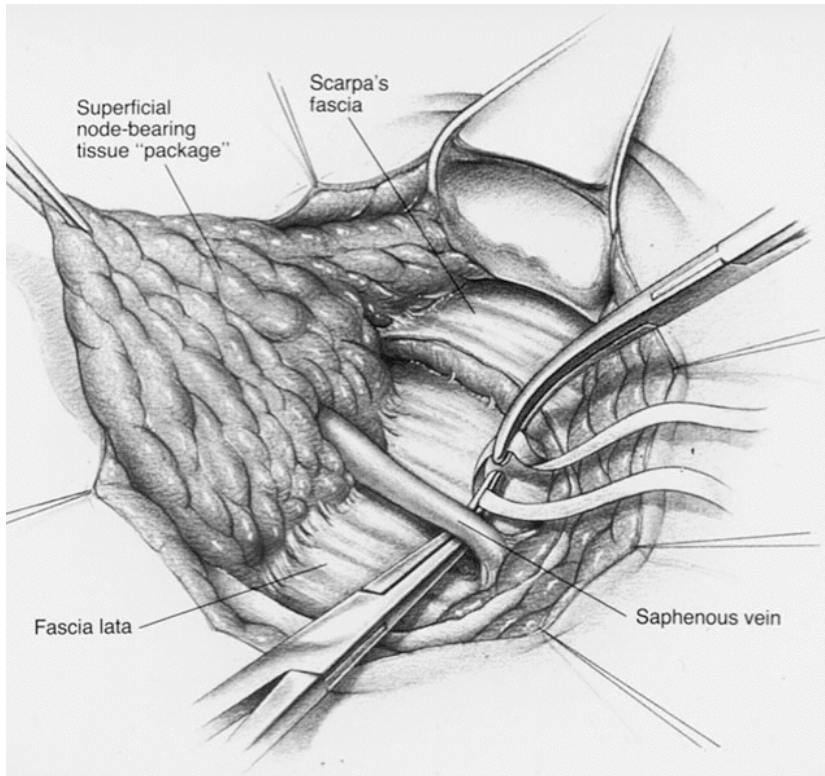
- patient placed in frog-legged position
- 10cm incision made ~1.5-2.0 cm below inguinal crease
- develop flap, just beneath Scarpa's fascia, 8cm superiorly and 6cm inferiorly
→ superior dissection to level of external oblique with exposure of spermatic cord
- **boundaries of LN dissection are inguinal ligament superiorly, femoral artery laterally, adductor longus muscle medially, and inferiorly to fossa ovalis (level of skin flap)**
- saphenous vein preserved although a number of branches draining into it may be ligated
- LN packet includes superficial and deep inguinal nodes

What are the potential complications after modified inguinal LN dissection?

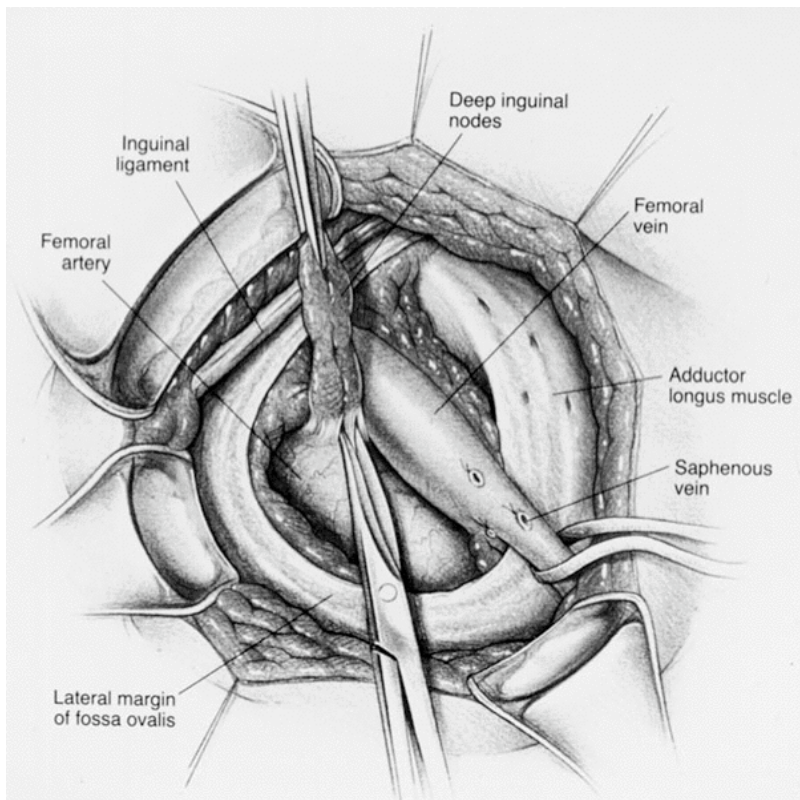
→ mostly minor complications that are self-limited

→ major complications rare

- seroma (25%)
- lymphorrhea (10%)
- wound infection (0-5%)
- skin infection (0-5%)
- lower limb edema (20%) } usually temporary



→ **Superficial Inguinal Nodes**



→ **Deep Inguinal Nodes**

What are the indications for radical ilioinguinal LN dissection?

- 1) resectable inguinal metastatic LNs
 - on presentation
 - after modified (+ve frozen section)
 - after period of surveillance
- 2) palliative procedure in patients with inguinal mets

What are the borders of the radical ilioinguinal LN dissection?

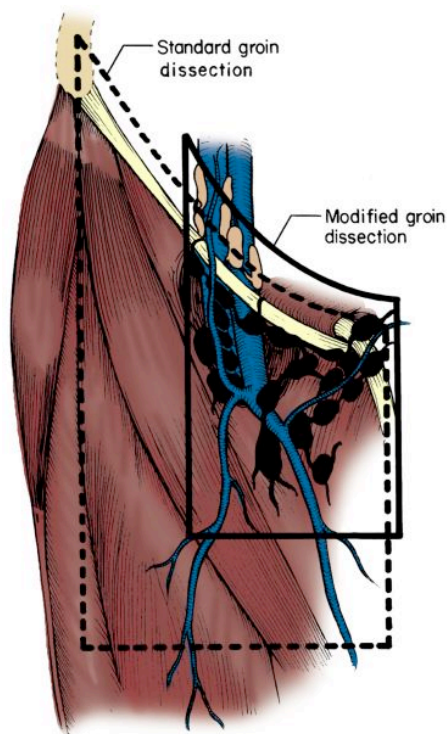
- superiorly } superior margin of external ring to ASIS
- laterally } ASIS to a point 20cm inferiorly
- medially } pubic tubercle to point 15cm down medial thigh

Describe the main steps of a radical ilioinguinal LN dissection?

- performed via an oblique incision approximately 3cm below and parallel to inguinal ligament
- involved skin over cancer excised if necessary via elliptical incision
- superior and inferior skin flaps developed in plane just below Scarpa's fascia
 - superior flap elevated up to 4cm above inguinal ligament
 - inferior flap elevated down to limit of dissection
- LN packet starts at inferior border of inguinal ligament and the long saphenous vein is identified and divided
 - if minimal metastatic disease, saphenous vein should be spared
- dissection deepened through fascia lata overlying sartorius laterally and adductor longus medially
- femoral artery and vein identified at apex of femoral triangle and dissection continued superiorly along femoral vessels
 - ligate any superficial cutaneous perforating arteries
- saphenous vein is divided at saphenofemoral junction and dissection continued superiorly to deep inguinal LNs medial and lateral to femoral vein until node of Cloquet at femoral canal (continuity with pelvic nodes)
- dissect anterior aspect of femoral vessels only and don't expose lateral surface of femoral artery } avoids injury to femoral nerve and profunda femoris artery
- after femoral triangle dissected, sartorius muscle mobilized from ASIS and transposed or rolled 180 degrees to cover femoral vessels } muscle sutured to inguinal ligament
- if necessary, close femoral canal by suturing shelving edge of Poupart's ligament to Cooper's ligament } don't compress external iliac vein or inferior epigastric vessels
- JP drain placed
- skin flaps sutured to exposed muscles to decrease dead space
- skin closed with staples
- bed rest for 2-3 days
- post-op TEDS +/- Abx

What are the options for closure of the inguino-femoral dissection?

- primary closure
- scrotal skin rotational flaps
- abdominal wall advancement flap
- myocutaneous flap (rectus abdominis, tensor fascia lata, vastus lateralis, omental, gracilis, etc)



What are the potential complications of radical ilioinguinal LN dissection?

- minor complications seen in ~50%
 - self-limited lymphocele
 - seroma
 - wound infection
 - wound necrosis
 - lymphedema
 - phlebitis
 - paresthesia
- **major complications occur in 5-20%**
 - debilitating lymphedema
 - flap necrosis
 - lymphocele requiring intervention
 - DVT/PE
 - femoral vessel erosion/injury
 - femoral nerve injury

What are the indications for pelvic lymphadenectomy?

- should be considered for certain patients
- poor prognosis for pelvic LN +ve disease → 15% 5yr survival
- 1) +ve superficial inguinal disease on frozen section
- 2) N1 disease with -ve pelvic LNs on pre-op studies
- 3) +ve pelvic LNs that respond to neoadjuvant chemo

Which nodes are included in the pelvic LN dissection?

- penile cancer mets to pelvic LNs DOES NOT OCCUR if ipsilateral inguinal nodes are -ve
 - distal common iliac
 - external iliac
 - obturator
- \ } carry dissection down to node of Cloquet
/

MALE URETHRAL CANCER

What are the RFs for urethral carcinoma?

- 1) chronic inflammation } STDs, urethritis, urethral strictures
- 2) HPV 16 (for SCC)
- 3) bladder Ca

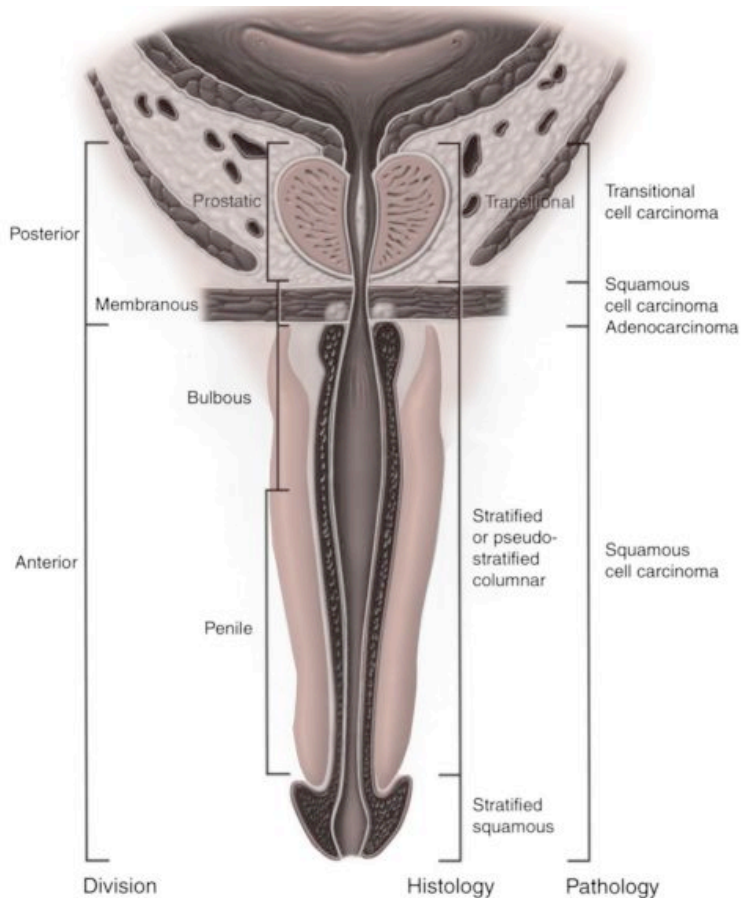
What is the most common presentation of urethral carcinoma?

- urethral bleeding
- palpable urethral mass
- obstructive voiding symptoms

Pathology

What types of epithelium are normally seen in the male urethra?

- prostatic } transitional cell
- membranous } stratified or pseudo-stratified columnar
- bulbar } stratified or pseudo-stratified columnar
- penile } stratified or pseudo-stratified columnar
- fossa navicularis } stratified squamous



What are the different histologic types of urethral carcinoma in males?

- **SCC (80%)**
- TCC (15%)
- adenocarcinoma, melanoma, lymphoma, paraganglioma, sarcoma, undifferentiated (5%)

What part of the urethra is most commonly involved?

- **bulbomembranous urethra (60%)** → 80% are SCC (10% TCC, 10% adenocarcinoma, etc)
- penile urethra (30% - mostly fossa navicularis) → 90% are SCC
- prostatic urethra (10%) → 90% are TCC

What are the routes of spread of male urethral carcinoma?

- direct extension } corpus spongiosum, periurethral tissues, etc
- lymphatic spread } regional LNs
- hematogenous spread } UNCOMMON except in advanced disease

What is the lymphatic drainage of the male urethra?

- anterior urethra } superficial and deep inguinal LNs
 } occasionally into external iliac LNs
- posterior urethra } pelvic LNs
 } **inguinal LNs involved in ~20% (almost always mets NOT inflammation)**

*** **anatomic ant & post urethra DOES NOT COINCIDE w/ oncologic ant & post urethral Ca** ***

→ anatomic anterior urethra = bulbar urethra and distal

→ oncologic anterior urethra = penile urethra and distal

Evaluation and Staging

What is involved in the work-up of male urethral carcinoma?

- history & physical exam
 - local symptoms & symptoms of mets
 - RFs (STDs, strictures, HPV, bladder Ca, etc)
 - palpation of external genitalia, urethra, rectum, and perineum
 - inguinal LN exam
- imaging
 - cystoscopy
 - CT abdo/pelvis
 - CXR
 - sigmoidoscopy if suspicion of rectal involvement
- blood/urine tests
 - CBC, lytes, creat, coag's, LFTs, ALP
 - urine cytology

What is the TNM classification of urethral cancer?

- T stage
 - Ta } papillary, polypoid, or verrucous carcinoma
 - Tis } CIS
 - T1 } invades subepithelial connective tissue
 - T2 } invades corpus spongiosum, prostate, or periurethral muscle
 - T3 } invades corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
 - T4 } invades adjacent organs
- N stage
 - N1 } mets to single LN ≤2cm
 - N2 } mets to single LN >2cm but <5cm or multiple LNs all <5cm
 - N3 } mets to LN >5cm
- M stage
 - M1 } distant mets

What are the common sites of urethral mets?

- liver
- lung
- brain
- bone

What is the T stage classification for TCC of the prostate?

- Tis-pu } CIS involving prostatic urethra
- Tis-pd } CIS involving prostatic ducts
- T1 } invades subepithelial connective tissue
- T2 } invades prostatic stroma, corpus spongiosum, or periurethral muscle
- T3 } invades corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
- T4 } invades adjacent organs (invasion of bladder)

Treatment

What are the main prognostic factors for urethral cancer? (AUA Update #12 – 2006)

- **tumour stage (most important)**
 - extent of urethral involvement
 - size at presentation
 - LN status
 - tumour location } distal is better
- **histopathology and grade DO NOT seem to influence prognosis**
- adenocarcinomas may have slightly worse prognosis

Does location of urethral tumour predict prognosis?

- **posterior urethral carcinoma is associated with poor prognosis**
- often associated with extensive local invasion and distant mets
- overall survival less than half of that associated with anterior urethral carcinoma

What are the treatment options for PENILE urethral carcinoma?

- 1) for select superficial, papillary, low-grade tumours } TUR
 } local excision
 } distal urethrectomy + PU
- 2) T2 in distal half of penis } partial penectomy with 2cm margin
 → excellent local control
- 3) proximal penile urethra } total penectomy
 → local recurrence rate of ~13%
- 4) SCC in situ of perimeatal glans } partial glansectomy + distal urethrectomy + reconstruction/PU
→ ilioinguinal lymphadenectomy indicated in presence of palpable inguinal LNs with no evidence of mets
➔ no benefit of prophylactic inguinal LN dissection however, even with high-risk disease

What are the treatment options for BULBOMEMBRANOUS urethral carcinoma?

- 1) radical cystourethrectomy + total penectomy } lowest recurrence rates & best long-term survival
+ pelvic LN dissection } may include pubic rami and adjacent UG diaphragm for better margins
- 2) TUR or local segmental excision with end-to-end anastomosis } ONLY for rare cases

Describe the main steps in a radical cystourethrectomy for urethral carcinoma.

- low lithotomy position
- standard cystectomy completed } preserve endopelvic fascia + anterior pubic attachments
- modified lambda or inverted U-shaped perineal incision made
- ischiorectal fossae are developed and a tunnel is bluntly dissected, just anterior to rectum, to connect the fossae
- inferior skin flap mobilized sharply off rectourethral muscle
- superior skin flap mobilized sharply off superficial Colles' fascia } extend bilaterally to adductor muscle
- circumferential incision of skin and dartos fascia at penoscrotal junction
- mobilization of corporal bodies proximally off superior aspect of inferior pubic rami to allow subsequent inferior pubectomy
 - don't carry dissection too proximally (avoid breaching anterior aspect of locally advanced Ca)
- penis passed down through perineal incision } if needed, scrotum can be divided in midline
- adductor muscles sharply divided bilaterally from length of inferior pubic ramus along medial margin of obturator foramen
- resection of subsymphyseal arch adequate in most } preserves stability of pelvic girdle & results in smaller pelvic floor defect
 - } entire symphysis may be resected for bulky lesion
- specimen delivered en bloc
- hemostasis secured then omentum mobilized to cover bowel
- rectus abdominis muscle flap used if large pelvic floor defect (eg after total pubectomy)
- myocutaneous flaps used to close large full-thickness perineal defects

What are the roles of RADS and CHEMO for urethral carcinoma?

- RADS } reserved for early-stage lesions of anterior urethra in patients refusing Sx
 - } preserves penis but results in skin ulceration or necrosis, urethral strictures, or chronic edema
 - CHEMO } used mainly for advanced stage or metastatic disease
 - } neoadjuvant or adjuvant settings
 - } MVAC for TCC and MTX, cisplatin, bleomycin for SCC
- RADS and CHEMO have been used in combination with Sx in a multimodal approach for patients with advanced stage or metastatic disease**

What are the management options for PROSTATIC urethral carcinoma?

- 1) TURP } superficial lesions only
- 2) cystoprostatectomy + total urethrectomy + pelvic LN dissection

What are the indications for pelvic LN dissection? (AUA Update #12 – 2006)

- +ve inguinal LNs
- proximal urethral disease
- advanced disease

How do you differentiate prostatic adenocarcinoma from poorly differentiated TCC infiltrating stroma?

- 1) PAP and PSAP staining } +ve in PCa only
 - -ve in 1% of PCa's
- 2) cytokeratin stains } +ve in TCC

Management of Urethra after Cystectomy

What is the recommended surveillance method for urethral recurrence post-cystoprostatectomy?

- urethral wash cytology (cutaneous diversion)
- voided cytology (orthotopic neobladder)
- if +ve cytology or symptoms (bleeding, etc) then proceed with urethroscopy
- CT or MRI for staging

How common is urethral cancer recurrence after cystoprostatectomy?

- 2-10% after cutaneous diversion } higher risk if prostatic stromal invasion or +ve distal urethral margin
- 0.5-4% after orthotopic neobladder } lower than for diversion (?biased population)
- 40% of recurrences are diagnosed within 1 yr after cystoprostatectomy
- but late recurrences occur so there is need for prolonged surveillance

What is the management of urethral CIS after orthotopic neobladder?

- urethral BCG } ineffective for papillary or invasive disease

Total Urethrectomy after Cutaneous Diversion

Describe the main steps of total urethrectomy after cutaneous diversion.

- exaggerated lithotomy position
- modified lambda or midline perineal incision made
- divide subcutaneous and bulbospongiosus muscle in the midline
- corpus spongiosum exposed and mobilized circumferentially near level of midbulbous urethra
- proceed to dissect corpus spongiosum distally, inverting penis, until the glans
- replace penis to N position and incise meatus and glandular urethra until the urethra freed
- proximal sharp dissection of urethral bulb carried out postero-laterally (stay close to bulb)
- detach urethra from corporal bodies anteriorly to level of departure of urethra from bulb
 - bulbar arteries are at 4- and 8-o'clock positions just inferior to perineal membrane
 - watch for adherence of bowel to superior surface of UG diaphragm from cystectomy
- completely excise proximal end of membranous urethra
 - frozen section can ensure clear margins
- drain left and brought out through perineum
- close bulbospongiosus muscle, subcutaneous tissue and skin with interrupted absorbable

Total Urethrectomy after Orthotopic Neobladder

Describe the main steps of a total urethrectomy after orthotopic neobladder.

- performed via abdominoperineal approach with patient in lithotomy position
- urethrectomy carried (as above) to level of membranous urethra
- abdominal exploration and mobilization of orthotopic neobladder performed to level of urethral anastomosis
- dissect out membranous urethra and the anastomosis
- cuff of neobladder taken to ensure margins
- specimen delivered through perineum
- urinary diversion is made } usually ileal conduit
 - } can use bowel from orthotopic neobladder
 - incise bowel along previous closure to ensure mesenteric blood supply
 - } may be able to convert to a continent cutaneous diversion

FEMALE URETHRAL CANCER

How common is female urethral carcinoma?

- **4x more common than M**
- only GU malignancy that is more common in women
- 85% occur in caucasians

What are the RFs associated with female urethral carcinoma?

- “Diverticulum Probably Has Cancerous BLIP”
- Diverticulum
 - Polyps
 - HPV infections
 - Caruncles
 - Bladder Ca
 - Leukoplakia
 - Irritation (chronic)
 - Parturition

What are the common sites of hematogenous mets?

- **often spreads systemically WITHOUT REGIONAL LYMPHADENOPATHY**
- **lung (most common)**
 - liver
 - bone
 - brain

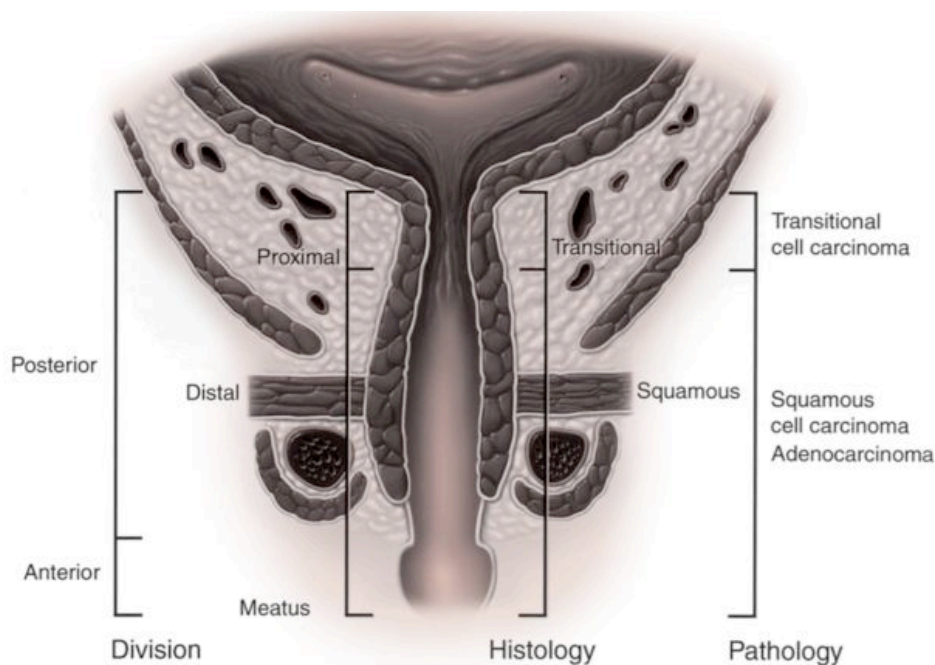
Anatomy and Pathology

What are the 2 parts of the female urethra?

- anterior urethra (distal 1/3)
 - **can be excised while maintaining urinary continence**
- posterior urethra (proximal 2/3)

What type of urothelium is seen in the female urethra?

- proximal 1/3 (half of posterior urethra) is transitional urothelium
- distal 2/3 is stratified squamous epithelium



What is the lymphatic drainage of the female urethra?

- anterior urethra and labia } superficial then deep inguinal LNs
 - posterior urethra } external and internal iliac and obturator LNs
- abN LNs palpable in 20-50% at time of Dx
- palpable LNs almost always represents mets

What are the different histologic types of urethral carcinomas in the female urethra?

- **50-70% are SCC**
 - 10-25% TCC (mostly proximal tumours only)
 - 10-25% adenocarcinoma (**more common in urethral diverticula**)
 - rare types include lymphoma, sarcoma, neuroendocrine carcinoma, melanoma, paraganglioma
- **distal tumours tend to be lower stage } distal tumours more common**
 → **proximal tumours tend to be higher stage } may extend into the bladder & vagina**

What is different about female urethral cancer arising in a urethral diverticulum? (AUA Update #12 – 2006)

- usually clear cell carcinoma } likely from remnants of müllerian ducts or from ectopic cloacal epithelium
- often located in distal 2/3 of urethra
- more frequent in black women

Diagnosis and Staging

What is involved in the work-up of female urethral carcinoma?

- history & physical exam
 - } local symptoms
 - } symptoms of mets
 - } RFs (diverticulae, polyps, HPV infections, caruncles, bladder Ca, etc)
 - } palpation of external genitalia, urethra, vagina, rectum, and perineum
 - } LN exam
- imaging
 - } cystoscopy
 - } CT abdo/pelvis
 - } CXR
- blood/urine tests
 - } CBC, lytes, creat, coag's, LFTs, ALP
 - } urine cytology

How advanced are urethral cancers in women at presentation?

- **30% have inguinal LNs at presentation** } more common in proximal & advanced disease
 } **90% are malignant**
- 20% have pelvic LN mets on presentation
- 15% develop mets during follow-up

What is the TNM classification of urethral cancer?

- same as in men
- T stage
 - T_a } papillary, polypoid, or verrucous carcinoma
 - T_{is} } CIS
 - T₁ } invades subepithelial connective tissue
 - T₂ } invades corpus spongiosum, prostate, or periurethral muscle
 - T₃ } invades corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
 - T₄ } invades adjacent organs
- N stage
 - N₁ } mets to single LN ≤2cm
 - N₂ } mets to single LN >2cm but <5cm or multiple LNs all <5cm
 - N₃ } mets to LN >5cm
- M stage
 - M₁ } distant mets

- ranges from 20-40%
- urinary incontinence
- urethral strictures
- urethral necrosis
- fistulae
- cystitis
- vulvar abscess
- cellulitis

What is the significance of inguinal lymphadenopathy in female urethral carcinoma?

- **often spreads systemically WITHOUT regional LN involvement**
- significant morbidity associated with inguinal LN dissection
- NO IMPROVED SURVIVAL after pelvic or inguinal LN dissection

List the 2 indications for groin dissection in female urethral carcinoma

- 1) +ve inguinal or pelvic LNs WITHOUT distant mets at presentation
 - 2) development of regional LNs during surveillance
- same dissection performed in men for penile cancer

What is the management of recurrent or radio-resistant urethral carcinoma in females?

- neoadjuvant rads + local excision } better than rads alone

Urethral Recurrence after Cystectomy in women

How common is urethral carcinoma in women undergoing cystectomy for bladder cancer?

- 1-13%
- frozen-section of urethral stump dictates whether orthotopic neobladder is feasible

How common is urethral recurrence after cystectomy + neobladder in women?

- 0-1%

What is the management of urethral recurrence after cystectomy + neobladder?

- urethrectomy + surgical resection of urethra-pouch anastomosis
 - conversion to cutaneous conduit using existing neobladder or conversion to continent cutaneous conduit if NO METS

- mainly for STGS only
- advantages
 - } can expand graft
 - } allows subgraft collections to escape
 - } allows graft to conform better to irregular graft host beds (eg testes)
 - } slightly better take

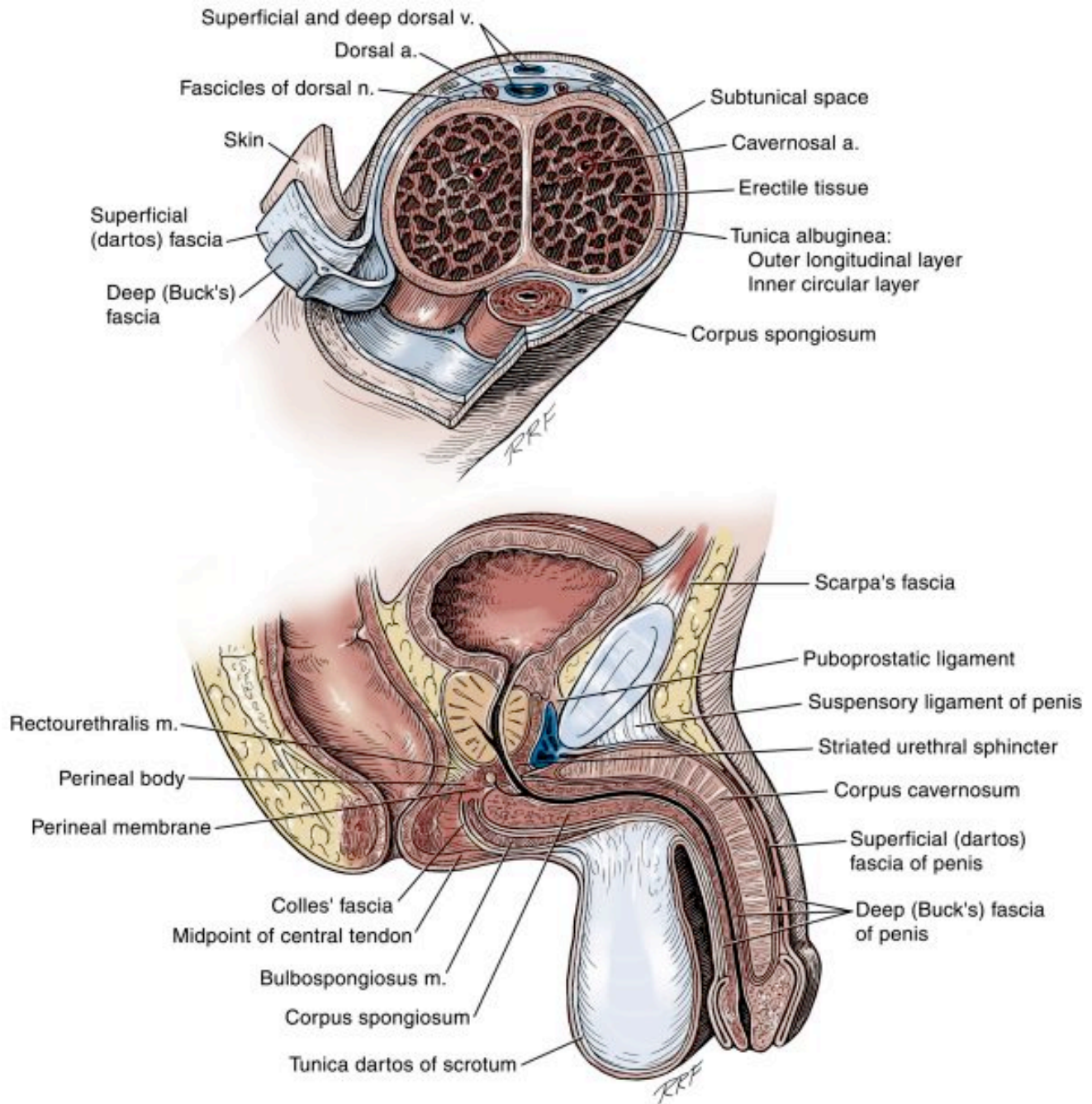
What tissues are commonly used in GU reconstruction?

- skin } dartos fascia skin island flaps used for urethral reconstruction
 - } good for defects in tunica albuginea of corpora cavernosa
 - } takes well
- bladder mucosa } epithelium + lamina propria
 - } good vascular characteristics (more perforators)
 - } **hypertrophic growth and dessication limits use in distal urethra**
- buccal mucosa } epithelium + lamina propria
 - } **optimal vascular characteristics with “wet” epithelial surface**
 - } good results for urethra
- posterior auricular FTSG (Wolff graft) } **good vascular characteristics**
- tunica vaginalis } essentially peritoneum
 - } poor results for urethra and good for only small defects of tunica albuginea in the corpora cavernosa
 - get aneurysmal dilation if used for larger defects
- vascular graft } not true graft
 - } survives by endothelial direct perfusion and re-establishment of vein wall blood flow by perfusion of vasa vasorum
 - } used for defects in tunica albuginea
- rectal mucosa } **proposed for urethra but no good literature**

What is a “flap”?

- excised tissue that is transferred **WITH blood supply** either preserved or surgically re-established
- classified based on vascular supply
 - random flap } no defined cuticular vascular territory
 - } survival depends on intradermal or subdermal plexuses
 - axial flap } defined vessel in base of flap
 - } peninsula, island, and microvascular “free” transfer flaps
 - } 3 main types include:
 - a) direct cuticular } based on vessel superficial to superficial layer of deep body wall fascia
 - } eg groin flap
 - b) musculocutaneous } based on vascularity to muscle
 - } overlying skin based on perforators
 - } eg gracilis flap
 - c) fasciocutaneous } based on vascularity to fascia
 - } overlying skin based on perforators
 - } eg penile dartos fascia flap
- also classified based on elevation technique
 - peninsular flap } vascular and cutaneous continuity of flap base left intact
 - island flap } only vascular continuity of flap base maintained
 - microvascular “free flap” } vascular and cuticular continuity interrupted
 - } needs microvascular re-establishment at recipient site

Anatomy of the Penis and Male Perineum



→ PENIS and PERINEUM

What are the different portions of the male urethra?

→ **WHO Stockholm 2002 } don't use anterior and posterior urethra**

- 1) fossa navicularis
→ stratified squamous
- 2) penile urethra (distal to ischiocavernosus musculature)
→ simple squamous
- 3) bulbous urethra (invested by bulbospongiosus muscle)
→ gradually changes from squamous to transitional
- 4) membranous urethra (surrounded by EUS)
→ transitional
- 5) prostatic urethra
→ transitional
- 6) bladder neck
→ transitional

What are the 5 sphincters found in relation to the male urethra?

- 1) BN
- 2) prostate (smooth muscle stroma)
- 3) external smooth muscle sphincter
- 4) external rhabdosphincter (EUS)
- 5) volitional muscles of recruitment around membranous urethra } not true sphincter

What glands empty into the male urethra?

- 1) prostate gland → equivalent to F Skene's glands
- 2) Cowper's glands (bulbourethral glands) → equivalent to F Bartholin's glands
- 3) glands of Littre (distal dorsal glands)

What are the glands of Littre?

- contribute mucus to ejaculate
- open into urethra along dorsal surface
- more numerous distally
- can form small diverticula called lacunae of Morgagni } often a large lacuna magna in dorsal wall of fossa navicularis

What is the dartos fascia?

- envelopes penis
- lies between skin and Bucks fascia
- lacks fat
- contains superficial arteries, veins, and nerves of penis
- continuous with tunica dartos of scrotum, Scarpa's fascia onto abdomen, Colles' fascia of perineum, and inserts at fascia lata

What is the blood supply to the skin of the penis?

- runs in dartos fascia
- **L and R superficial external pudendal arteries** } branch off 1st portion of femoral artery
→ runs dorsolaterally and ventrolaterally in shaft of penis (**superficial penile artery**)
→ gives off fine branches to skin, forming rich subdermal vascular plexus
- penile skin good for urethral reconstruction
→ very thin
→ mobile
→ good vascular supply
- veins follow arteries

What is the blood supply to the scrotum?

- runs in tunica dartos
- **posterior scrotal artery** } superficial vessel from deep internal pudendal artery ("IPP BP,CP")
→ supplies scrotal wall and ventral penile skin

What is the lymphatic drainage of the penis?

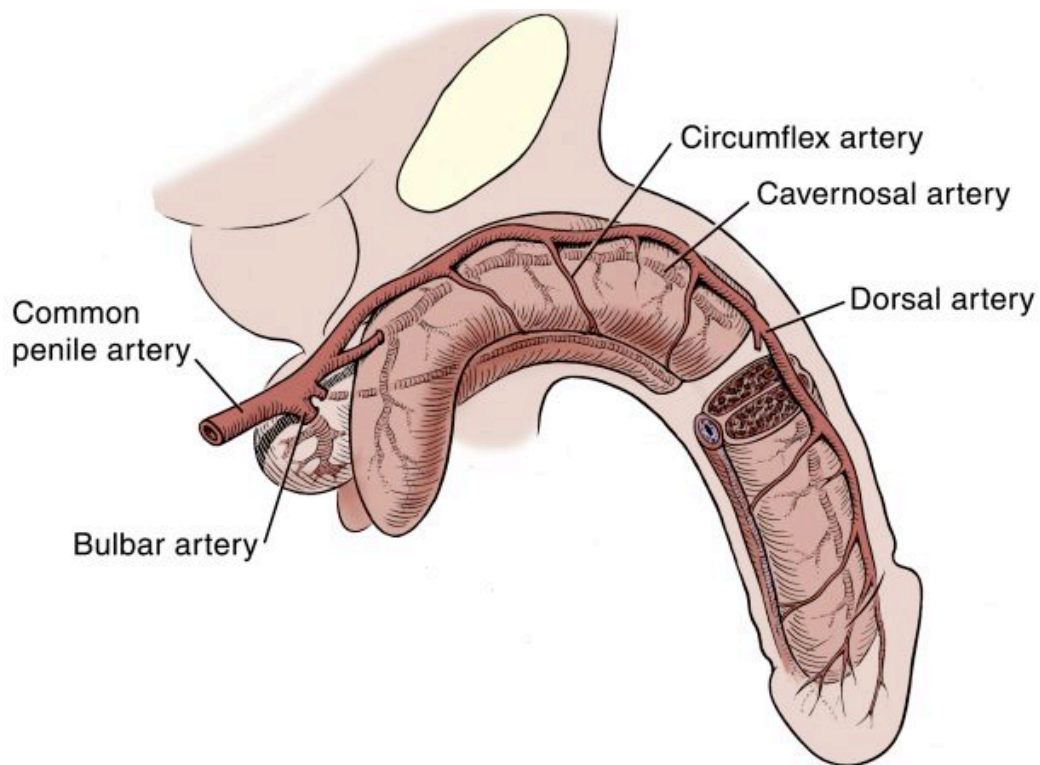
- glans drains into area of frenulum
- lymphatics then circle to dorsal aspect of corona then travel along dorsum of penis to
drain into deep inguinal LNs of femoral triangle
- travels beneath Buck's fascia

What is the arterial supply to the penis?

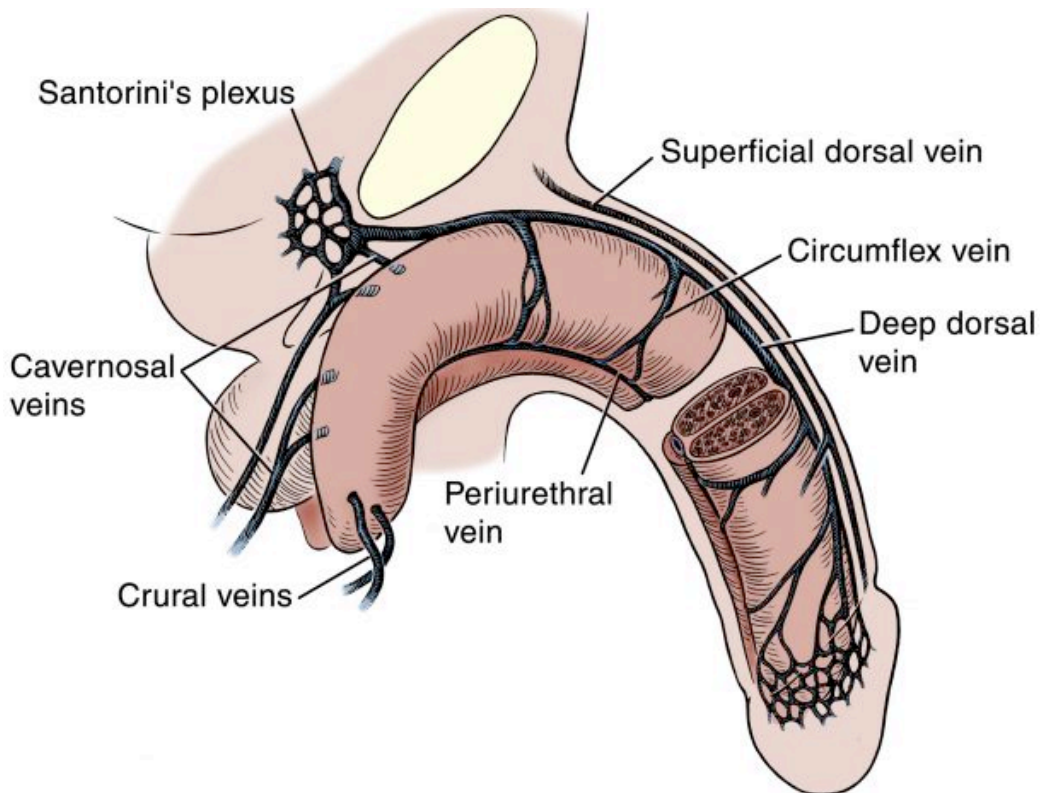
- internal iliac artery (anterior branch – "OSIOMUII")
→ internal pudendal artery ("IPP BP,CP")
→ common penile artery (end of internal pudendal)
→ 3 terminal branches:
 - a) **bulbourethral artery** } enters bulbospongiosus
 - b) **cavernosal artery** } gives off helicine arteries w/in corpora cavernosa
 - c) **dorsal artery** } gives off circumflex arteries

What is the venous drainage of the penis?

- 1) superficial } veins in dartos fascia on dorsolateral aspect
} unite at base of penis to form **superficial dorsal vein**
} superficial dorsal vein **drains into L saphenous vein** (rarely into R)
- 2) intermediate } deep dorsal and circumflex veins lying within and under Buck's fascia
} emissary veins from corpora cavernosa go through tunica albuginea
emerging dorsolaterally into circumflex veins or deep dorsal vein
} **circumflex veins** drain into deep dorsal vein or periurethral vein ventrally
} **deep dorsal vein** drains into **periprostatic (Santorini's) plexus**
- 3) deep } **crural veins** come from midline, between crura, draining into **deep dorsal vein**
or **periprostatic plexus**
} **cavernosal veins** come from proximal crura and drains into **internal pudendal vein**
} **bulbar veins** also drain into internal pudendal vein



→ ARTERIAL SUPPLY OF PENIS



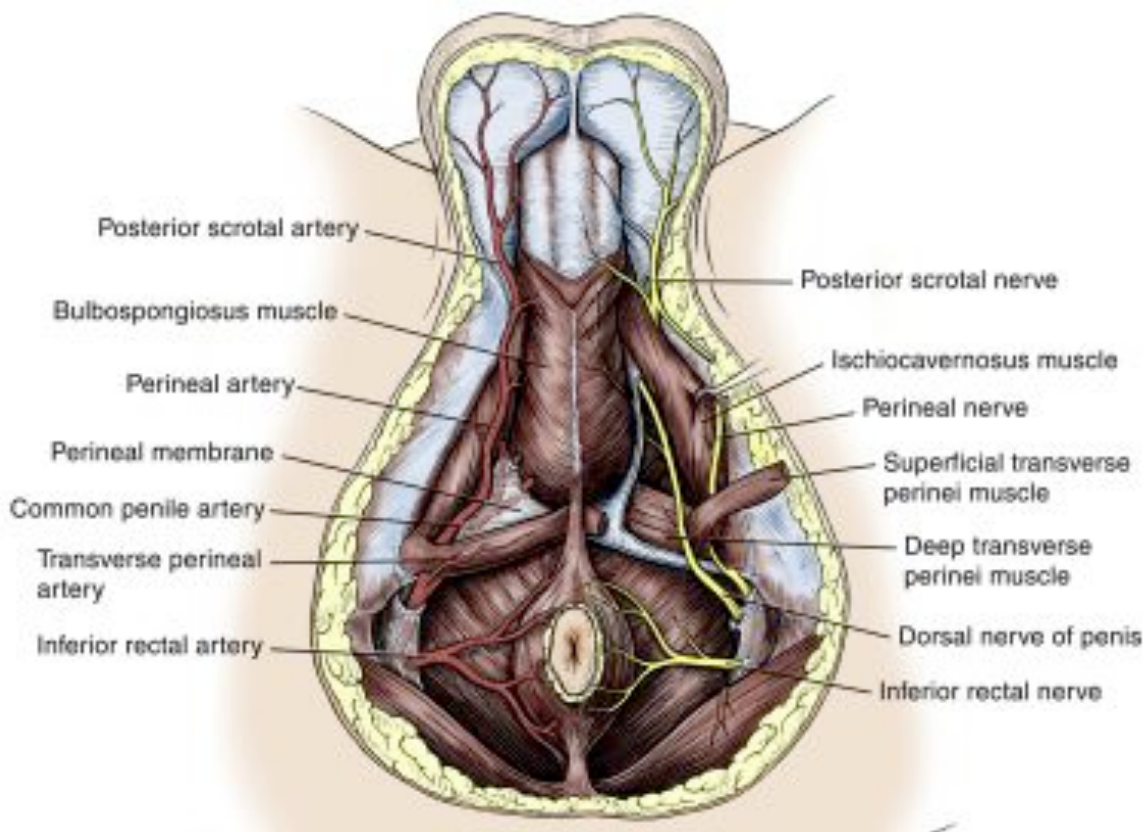
→ VENOUS DRAINAGE OF PENIS

What is the innervation of the penis?

- 1) pudendal nerve } somatic motor and sensory
 } **runs in Alcock's canal**
 } gives off dorsal nerve of penis
- 2) **cavernosal nerve** } autonomic nerves
 } run dorsomedial to cavernosal arteries
 } comes from **pelvic plexus**
 → parasympathetics (S2-4) via pelvic nerve
 → sympathetics (T11-L2) via hypogastric nerve

What are the borders of the perineum?

- anterior } pubic arch and circulate ligaments of pubis
 - posteriorly } tip of coccyx
 - laterally } inferior rami of pubis & ischium
- transverse line b/w ischial tuberosities divide perineum into anterior triangle & posterior anal triangle



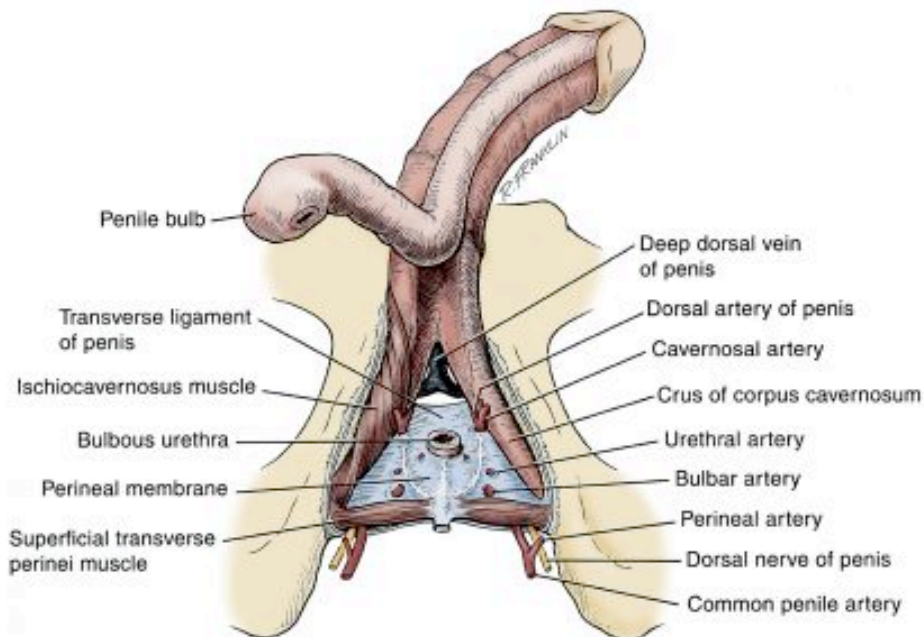
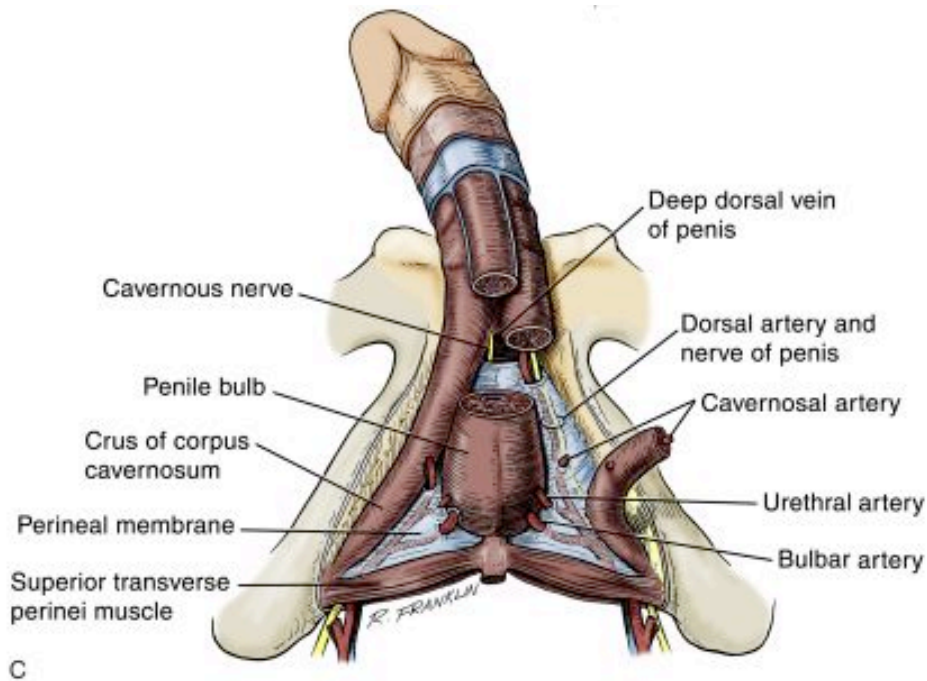
→ MALE PERINEUM

What is contained within the male superficial perineal space?

- **superficial transverse perineii muscles**
- continuation of **corpora cavernosa & crura** } covered by **ischiocavernosus muscle**
- proximal part of **corpus spongiosum & bulbar urethra** } covered by **bulbospongiosus muscle**
- branches of **internal pudendal vessels**
- **pudendal nerves**

List muscles of the perineum that insert in the perineal body?

- fibers from anterior portion of **external anal sphincter**
- **superficial transverse perinei** muscles
- **deep transverse perinei** muscles
- posterior fibers of **bulbospongiosus**
- anterior fibers of **levator ani**
- **rectourethralis**
- **external urethral sphincter**



→ MALE PERINEUM

What are some of the surgical principles of GU reconstructive surgery?

- bipolar cautery decreases collateral injury
- use of fine, delicate instruments
- use smallest caliber suture as possible
- absorbable suture for all urethral surgery
- use of exaggerated lithotomy position for only the minimal time necessary
- **goals are to minimize tissue damage and maximize wound healing**

SELECTED PROCESSES

What are urethral hemangiomas?

- rare, benign, abnormally dilated blood vessels
- usually presents w/ **hematuria or bloody urethral discharge**
- can occasionally present with obstructive symptoms
- Dx is made at cystoscopy } **common location is urethral meatus**
- usually persistent although can occasionally regress on own

$R_x \rightarrow$ depends on size and location

- if asymptomatic } observe
- if symptomatic } complete excision with urethral reconstruction
- } fulguration with laser (KTP, YAG, etc) if small lesion

What is Reiter's syndrome?

- **classic triad of arthritis + conjunctivitis + urethritis** } usually not present
- some have diarrhea episode preceding arthritis
- urethral involvement is usually mild, self-limiting, and a minor portion of disease
 - if severe, can cause severe inflammation resulting in stricture disease
- can get glanular lesion in 10-20% } **circinate balanitis**
 - diagnostic of Reiter's
 - shallow, PAINLESS ULCER with grey borders

Rx \rightarrow observation if mild

- if severe strictures, then make PU and excise entire distal urethra

What is BXO?

- balanitis xerotica obliterans } **lichen sclerosis at atrophicus** is preferred term
- histologic examination of tissue reveals:
 - a) hyperkeratosis
 - b) homogenization of collagen in papillary dermis (superficial layer)
 - c) stromal edema
 - d) lymphatic & histiocytic infiltrate
- appears as white plaque that can involve prepuce, glans, urethral meatus, and fossa navicularis
- **most common cause for meatal stenosis**
- Dx is made on Bx
- **may be associated with spirochete infections (*Borrelia burgdorferi*)**
- urethral stricture disease may develop from high-pressure voiding which forces urine into glands of Littre, resulting in inflammation
- **pre-malignant lesion } may develop penile SCC**

Rx → Cx may be curative if only involving foreskin

- topical steroids and Abx
- meatal dilators
- surgery for severe meatal stenosis and/or stricture disease
 - use only buccal grafts for urethra strictures } BXO is a skin disease
 - penile skin flaps to be avoided, unless only confined to meatus and fossa navicularis



→ BXO

What is the management of urethrocutaneous fistulae?

- may be complication of urethral surgery, secondary to periurethral infection associated with inflammatory strictures, or secondary to treatment of a urethral growth
 - **early post-op fistula often d.t. poor local healing, hematoma, infection, or tension**
 - **late post-op fistula may be d.t. distal obstruction & high-pressure voiding**

→ must treat fistula AND cause of fistula

1) small fistulae

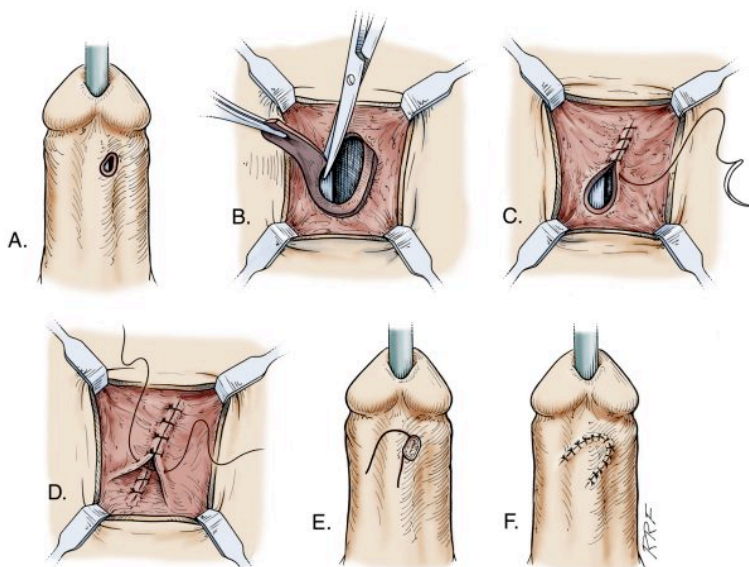
- may close spontaneously with aggressive local care & continued urinary diversion
- repair should be delayed for 6 months
- excision of skin around fistula + closure with 6-0 or 7-0 absorbable suture
- closure of subsequent layers to avoid superimposing suture lines
- urethral stent +/- S/P tube

2) large fistulae

- excision of skin around fistula + penile skin flap
- urethral stent + S/P tube

3) watering pot perineum

- S/P tube
- I&D of any abscesses
- widely excise fistula tracks
- wait 4-6 months before repair
- flap reconstruction VS staged graft procedure



→ URETHROCUTANEOUS FISTULA REPAIR

What are the causes of urethral diverticulum?

→ **presents with 3 D's } dribbling, dysuria, dyspareunia**

- congenital diverticulum is a transitional cell-lined pouch
- different etiologies include:
 - 1) distension of a segment of urethra
 - 2) attachment of a structure to the urethra by a narrow neck (eg mullerian remnant)
 - prostatic urethral tic (usually occurs in proximal hypospadias)
 - 3) incomplete development of urethra with only a defect in the ventral wall
 - anterior urethral tic
 - 4) straddle injury with resultant intraspongiosal hematoma
 - anterior urethral tic
 - 5) giant cystic dilation of Cowper's ducts
 - 6) female dilation of periurethral glands, following birth trauma
- diagnosis made with US, MRI, cystoscopy

Rx → excise urethral diverticulum

→ close neck through vertical or U-shaped vaginal incision

→ don't overlap suture lines

What is urethral amyloidosis?

- rare but **on DDx of urethral mass**
- presents with hematuria, dysuria, or urethral obstruction
- Dx made on cysto + Bx
- progression and recurrence are rare

Rx → based on symptoms only

→ observation and treat strictures prn

What is balanoposthitis?

- severe balanitis in the setting of tight phimosis
- results in preputial cavity abscess

Rx → emergency dorsal slit

What is the cause of meatal stenosis?

→ kids

- congenital association
- Cx with resultant ammoniacal meatitis (results in healing with membrane across ventral portion of meatus) } get classic stream that points up

Rx → ventral urethral meatotomy

→ cotrimoxazole cream + meatal dilator

→ adults

- inflammation (eg BXO)
- infection (eg STDs)
- trauma

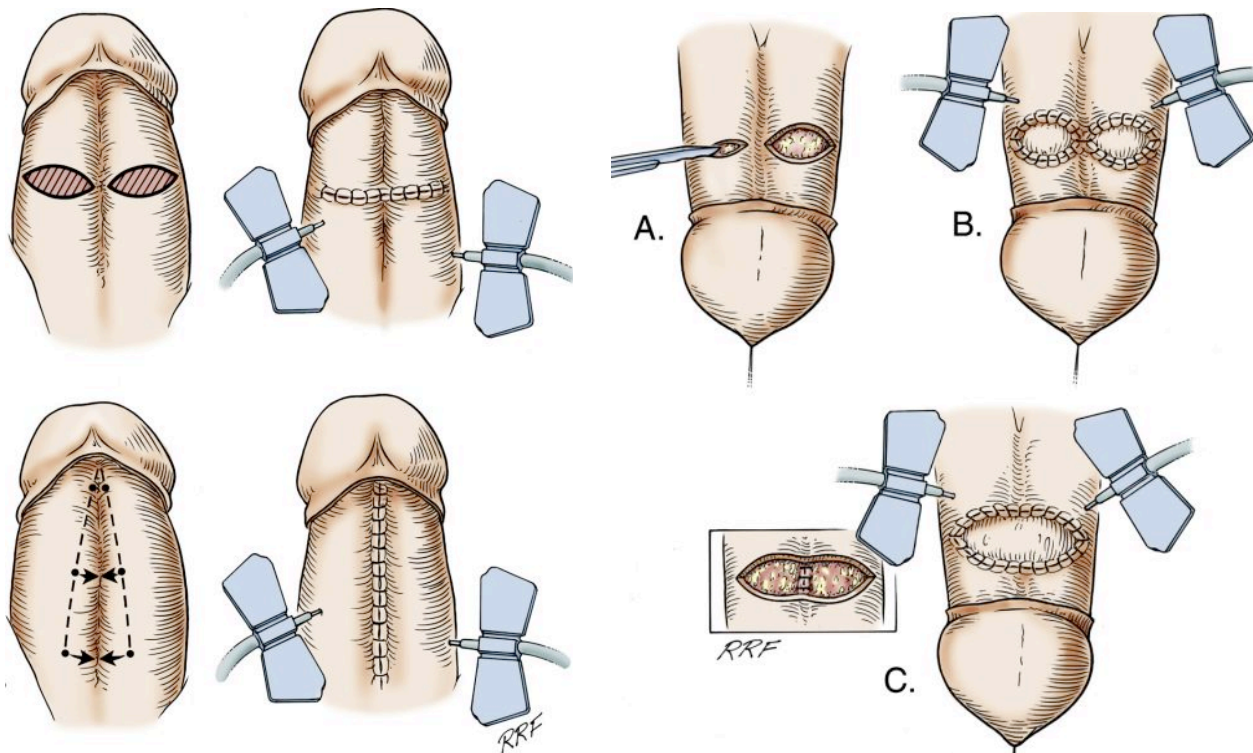
Rx → ventral or dorsal urethral meatotomy

→ cotrimoxazole cream + meatal dilator

What are the potential complications of Cx?

- bleeding
- infection
- urethrocutaneous fistula
- excess skin removed
- penile loss from overzealous use of monopolar cautery
- glanular transection (rare)
- urethral injury
- meatal stenosis

→ **penile abnormality (eg hypospadias, chordee) that may need penile foreskin for repair is a contraindication to Cx**



→ REPAIR OF CHORDEE (Nesbitt, Koff's, dorsal inlay graft)

PENETRATING TRAUMA TO THE PENIS

What are the goals of repairing penetrating penile trauma?

- exploration and attempted immediate anatomic repair
- placement of S/P tube with extensive urethral injury
- primary reconstruction of small, low-velocity wounds
- diversion and delayed reconstruction of larger, high-velocity wounds
- management of delayed sequelae such as urethral strictures, penile curvature, and fistulae

What is the management of penile amputation?

- **if acute presentation, microvascular replantation is treatment of choice**
 - if no micro surgeon available, transfer to another institution
 - clean and wrap amputated portion in sterile NS-soaked gauze then put in sterile bag
 - **can re-implant up to ~18hrs**
 - 2 layer spatulated urethral anastomosis over catheter
 - **microvascular repair of dorsal vein, artery, and nerves preferred**
 - repair tunica albuginea with interrupted sutures
 - coverage with native skin
 - S/P tube
 - if microvascular surgeon unavailable, replantation using McRoberts principles +/- leeches
- if amputated portion is unavailable,
 - close corporal bodies with 4-0 PDS
 - spatulate urethral meatus to tunica
 - cover penile shaft (+/- STSG) } can also bury shaft under skin of scrotum
 - delayed phallic reconstruction or penile reconstruction
- consider psych consult if self-inflicted (most cases ~65-90%)

What is the management of de-gloving injuries of the penis?

- tear is deep to elastic dartos fascia but superficial to Buck's fascia
 - not many vessels in this space
 - bleeding usually not a problem
- dress wounds in sterile saline-soaked gauze
- **delay repair by ~24hrs to define extent of damage**
- **early/immediate coverage of penis with STSG**
- pexy testes in midline and cover with meshed STSG } graft placed directly on testes after opening parietal tunical vaginalis
- if testes avulsed, don't attempt to replant
- another option is to bury shaft of penis in subcutaneous tunnel on abdomen and bury testes in subcutaneous thigh pouches

What is the management of genital burns?

- ability to reconstruct damage depends on how well normal structures have been maintained after the acute injury
- **careful debridement is the rule in acute management (less aggressive due to unique vascularity of genital tissue)**
- urethral injuries often devastating } may need PU
- penis often incarcerated in contracted scar tissue } gracilis musculocutaneous flap to release shaft then STSG to cover it
- reconstruction often requires a number of stages

What is the management of radiation trauma to the penis?

→ seen in 2 patient populations:

1) therapeutic Rads for penile lesion

- can cause chronic suppurative gangrene
- can also cause urethral injury
- success of repair largely depends on radiation damage to adjacent structures
- Rx → partial penectomy + later reconstruction

2) pelvic radiation

- get chronic lymphedema, cellulitis, weeping of fluid, or lymphangiectasia
- lymphedema involves dartos fascia and dermal layer of skin
- posterior and lateral scrotum often not involved
- glans almost never involved
- Rx → prolonged ABx for cellulitis
 - removal of dartos fascia and skin (for lymphedema in penis) + STSG
 - removal of Colles' fascia-tunica dartos and skin (for lymphedema in scrotum) + meshed STSG
 - avoid FTSG and local skin flaps } reaccumulation of lymphedema because has lymphatic channels

URETHRAL STRICTURE DISEASE

What is the difference between anterior and posterior urethral stricture disease?

- anterior } scarring process that usually involves some degree of spongiofibrosis
- posterior } obliterative process resulting in fibrosis
 - } usually the result of distraction injury (trauma or RP)
 - } posterior disease is **not true “stricture disease” as per WHO**

What is the relation of the urethra to the corpus spongiosum?

- proximally, urethra is closer to dorsum
- moving distally, urethra becomes more central within corpus spongiosum

What is the blood supply to the corpus spongiosum?

- dual blood supply
- proximal } **bulbourethral artery** (via common penile a., terminal branch of int. pudendal)
- retrograde } **dorsal arteries via glans penis** (another branch of common penile)

What are the causes of anterior urethral strictures?

- idiopathic/congenital
- inflammatory } BXO (lichen sclerosis et atrophicus)
 - } STDs (eg gonococcal urethral strictures)
 - } TB
- ischemic } radiation
- traumatic } saddle trauma (bulbous urethra)
 - } iatrogenic injury (instrumentation)
 - } penetrating injury
- malignancy } urethral Ca

What is the presentation of urethral stricture?

- obstructive voiding symptoms
- AUR
- UTIs
- prostatitis/epididymitis
- hematuria

What is the approach to assessing a urethral stricture?

- 1) history } infections, trauma, voiding symptoms, instrumentation, STDs
 - 2) physical exam } depth and density (spongiofibrosis)
 - 3) imaging } cystoscopy, RUG, U/S, MRI
 - } location, length, depth, density
- depth and density hard to determine objectively
 - need to assess urethra proximal and distal to stricture with endoscopy and bougienage to ensure all involved urethra is excised
 - high-pressure voiding may keep proximal segment patent, making it seem uninvolved
 - placement of S/P for 4-6 weeks before assessment may allow urethra to stabilize, making it easier to delineate all diseased areas of urethra

What are the management options for urethral stricture disease?

- step-ladder approach OLD AND NOT CONSIDERED IDEAL APPROACH
- need to discuss goals with patient } repeat dilations, etc VS more definitive detailed surgery
- 1) catheters } indwelling vs CIC vs S/P
- 2) dilation
- 3) cold VIU or laser VIU
- 4) open reconstruction (urethroplasty)



→ NORMAL RUG } EUS found 1/3 of the way up obturator foramen, veru = filling defect

What is the role of DILATIONS for urethral strictures?

- **may be curative if no spongiositis**
- goal is to stretch the scar without producing more scar } bleeding means torn rather than stretched
- urethral balloon dilation safest method
- **repeated dilations and VIU decreases success rate of urethral reconstruction**

What is the role of VIU for urethral strictures?

- incision through scar to healthy tissue
- goal is for lumen to heal enlarged (epithelium heals by secondary intention)
 - want epithelialization before wound contraction
- single incision at 12-o'clock
 - urethral arteries at 3- and 9-o'clock
 - deep incisions can penetrate through corpora spongiosum and enter intracanal space, leading to ED (veno-occlusive disease) } especially proximally
- **curative in only ~20 to 30% } long term success more likely w/ short strictures (<1.5cm) in bulbous urethra without dense, deep spongiositis**
- prolonged catheterization not beneficial (6 weeks same as 3-7 days)
- CIC may have some benefit
- urethral stents used to oppose wound contraction have limited success
 - eg UroLume, Memokath
- **repeated dilations and VIU decreases success rate of urethral reconstruction**

What are the contraindications to VIU?

- length >1.5cm
- membranous urethral stricture post-TURP
- abscess/UTI
- bleeding diathesis
- complete obliteration of urethra

What are the potential complications of VIU?

→ early

- bleeding } usually associated with erections post-op
- UTI/periurethral abscess
- extravasation of irrigation fluid into peri-spongiosal tissue } use NS fluid
- false passage

→ late

- **recurrence of stricture (most common complication)**
- ED (from local cavernosal veno-occlusive disease)
- incontinence (damage to EUS)
- urethral diverticulum
- chordee/Peyronie's

What is the role of LASER VIU for urethral strictures?

- CO₂, argon, KTP, Nd:YAG, Holmium:YAG, excimer lasers
- ideal laser totally vaporizes tissue, causes no peripheral destruction & isn't absorbed by water
 - CO₂ ideal but requires gas scope } risk of CO₂ PE
 - KTP and Ho:YAG next best
- mixed results to date } no significant benefit over cold-knife VIU

What are the specific contraindications to the use of a UroLume urethral stent?

Y"

- Cancer (urethral)
- Prostatic stent } can't have both prostatic and urethral
- Perineal urethrostomy
- Pendulous urethral strictures } penile or meatal
- UTI (active)
- Skin graft used for prior urethral reconstruction
- Strictures associated with deep Spongiofibrosis } ie PFUD
- Young patients (relative)

What is the role of OPEN URETHROPLASTY for urethral strictures?

- 1) excision + reanastomosis } **most dependable technique (GOLD STANDARD)**
 - } total excision of fibrosis, widely spatulated & tension free anastomosis
 - } vigorous mobilization of corpus spongiosum is the key
 - } **traditionally for strictures <2cm but can use for up to ~4cm**
- 2) graft reconstruction } primary VS staged
 - primary (bladder, buccal, and rectal mucosa and FTSG)
 - staged (STSG, buccal mucosa, poster. auricular FTSG)
 - for penile strictures, FTSG preferred over STSG due to chordee formation (contractures of STSG)
 - extra-genital STSG better than extra-genital FTSG } better take
 - } incisional VS excision
 - excisional augmented anastomosis likely better
 - } onlay VS tubularized
 - onlay better
 - dorsal & lateral likely better than ventral onlay + spongioplasty
 - tubularized only as last option } grafts not as good as flaps
 - } Monseur technique + Barbagli modification
 - dorsal incision + dorsal graft onlay + edges of urethra sutured to edges of graft
 - } **most successful in bulbous urethra** (covered by bulbospongiosus muscle)
- 3) local flap reconstruction } primary
 - } incisional VS excision
 - excisional augmented anastomosis likely better
 - } onlay VS tubularized
 - onlay better
 - tubularized only as last option } flaps better than grafts
 - } penile dartos fascia flap VS scrotal tunical dartos island flap
 - penile skin preferred when possible } better results
 - dorsal transverse (Duckett)
 - ventral longitudinal +/- "hockey stick" (Orandi), ventral transverse, and ventral circular
 - } flaps should be based laterally when possible
 - } ideal to use redundant, non-hirsute, genital skin
 - } important to consider nature of flap tissue, the vasculature of the flap, and the mechanics of flap transfer
- 4) urinary diversion } PU
 - } BN closure + complete diversion

What are the advantages of penile skin over scrotal skin for urethroplasty?

- hairless
- better waterproof characteristics } less dermatitis and cicatrisation due to urine
- easier to form into uniformly sized urethra
- decreased risk of diverticula formation

What are the indications for the different methods of urethral reconstruction?

→ penile urethral stricture repair associated with high complication rate

- 1) excision + reanastomosis } 1-2cm strictures (likely up to 4cm)
 - } single-layer anastomosis preferable
 - } **can excise longer segments if stricture proximal (closer to membranous urethra) & if young (compliant tissue)**
- 2) graft reconstruction } good for long segments of stricture
 - } can be used for any segment of anterior urethra but likely best suited for **proximal reconstruction**
 - } **onlay better than tubularized**
 - } placement of graft directly on corpora cavernosa is suboptimal due to lack of graft mobility & potential for chordee if graft contracts a lot
 - } **dorsal & lateral onlay likely better than ventral onlay**
 - lateral has advantage of cutting into corpus spongiosum where it is thinner (less bleeding) & suturing graft to muscle (better take)
 - ventral onlay with spongioplasty requires normal corpus spongiosum adjacent to area of stricture
- 3) flap reconstruction } good for long segments of stricture and complex re-do's
 - } **avoid in BXO**
 - } best suited for **distal reconstruction**
 - } **onlay better than tubularized**
 - } **dorsal & lateral onlay likely better than ventral onlay**
 - lateral has advantage of cutting into corpus spongiosum where it is thinner (less bleeding) and suturing graft to some muscle (better take)
 - ventral onlay with spongioplasty requires normal corpus spongiosum adjacent to area of stricture

When might a flap reconstruction be preferred over a graft reconstruction?

- radiation strictures
 - patients with multiple operations
 - distal strictures
- ➔ **avoid for BXO } staged buccal graft preferred**

What are the methods used to mobilize the corpus spongiosum?

- dissection of Buck's fascia to improve compliance
- development of intracanal space
- detachment of bulbospongiosus from perineal body

How successful is open urethroplasty?

- excision + primary reanastomosis } almost 100% at 1yr
- } DOES NOT DETERIORATE over time
- graft or flap reconstruction } 95% at 1yr
- } deteriorates with time
- } complication rate higher with penile urethral strictures
- graft reconstruction equivalent to flap reconstruction } graft reconstruction easier though
- much lower success rates for BXO } staged buccal graft is preferred method

What are the potential complications of urethroplasty?

- recurrence of stricture
- loss of graft/flap
- urethrocutaneous fistula
- chordee (graft shrinkage)
- diverticulum
- UTI/abscess
- bleeding/hematoma
- ED } 2-5% → more common with longer segment reconstructions
- chronic pain
- incontinence
- Peyronie's disease

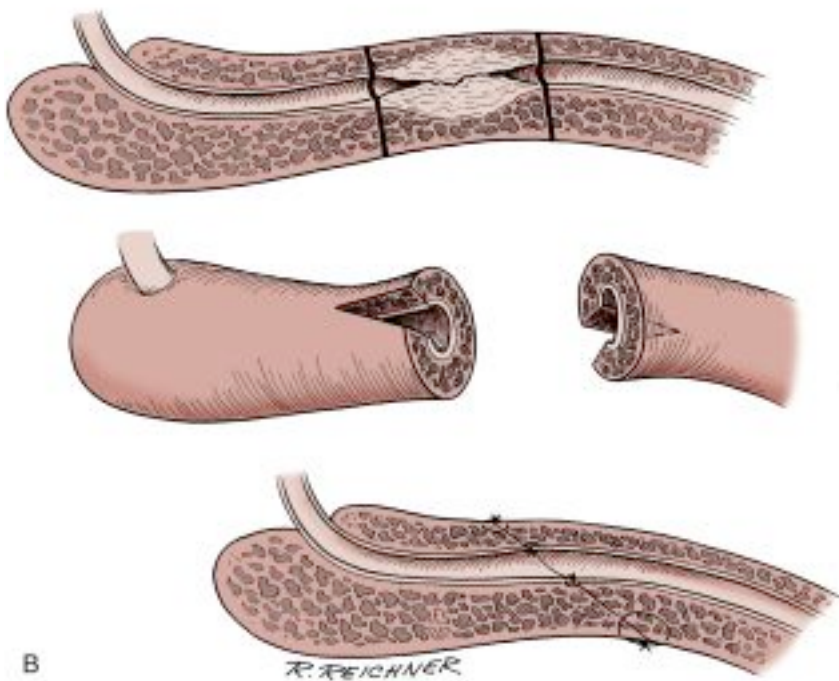
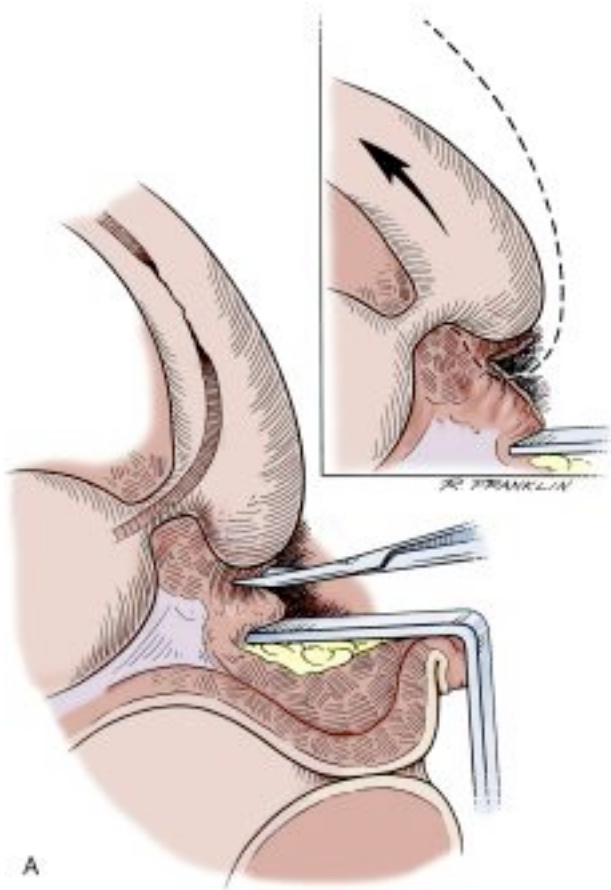
Describe the technique of a 2-stage mesh graft urethroplasty (Webster).

A) 1st stage

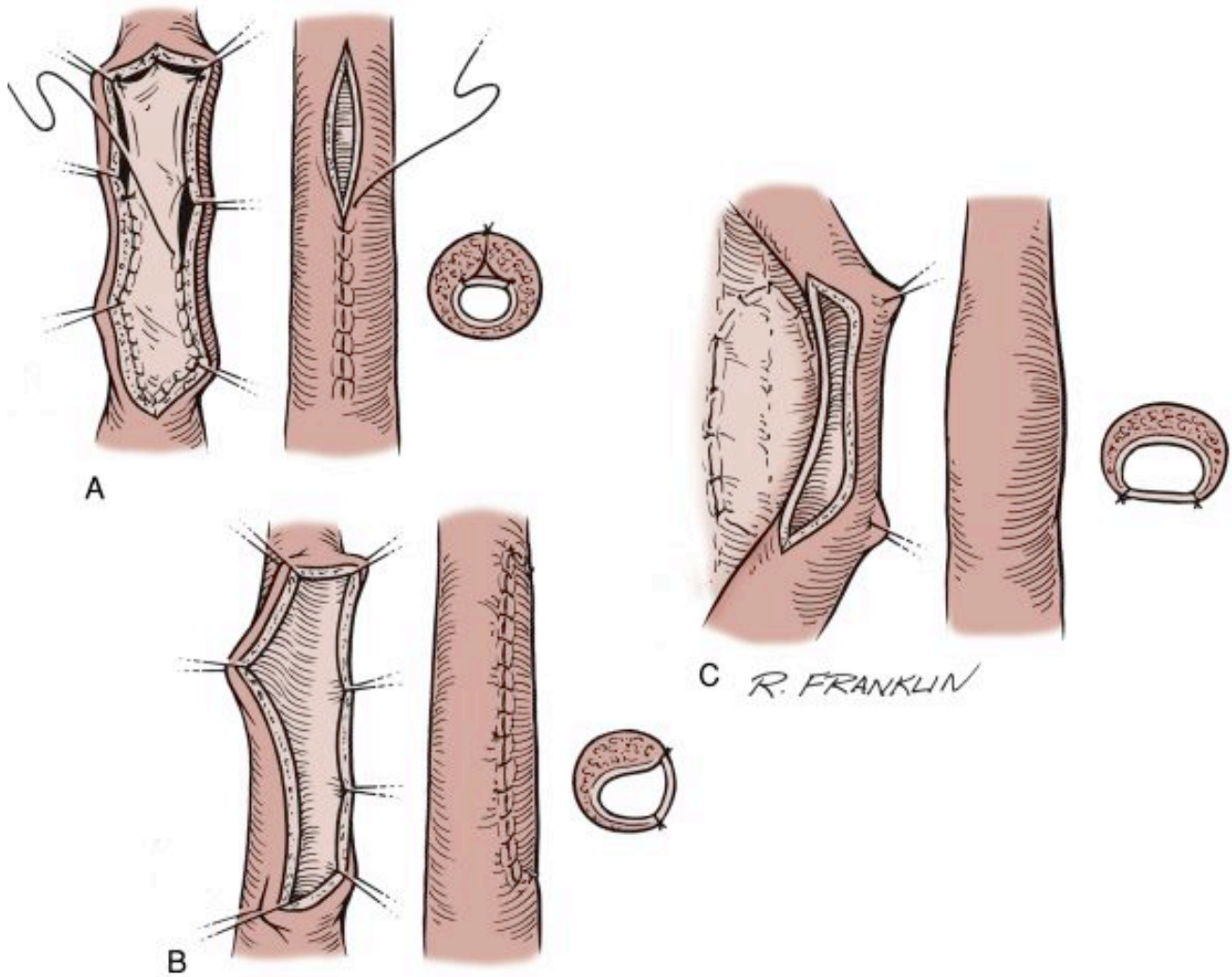
- strictured urethra is excised completely
- dartos fascia mobilized & brought in to cover tunica albuginea and scar in defect w/ vascularized tissue
 - if graft placed immediately on tunica albuginea, can't mobilize in 2nd stage to create tube
- STSG harvested from buttocks or inner surface of the thigh and meshed
 - placed in site of excised urethra as open-faced graft, w/o expanding mesh
- graft covered w/ gauze & bolster of batting w/ tie-over sutures, Foley left in proximal urethra

B) 2nd stage

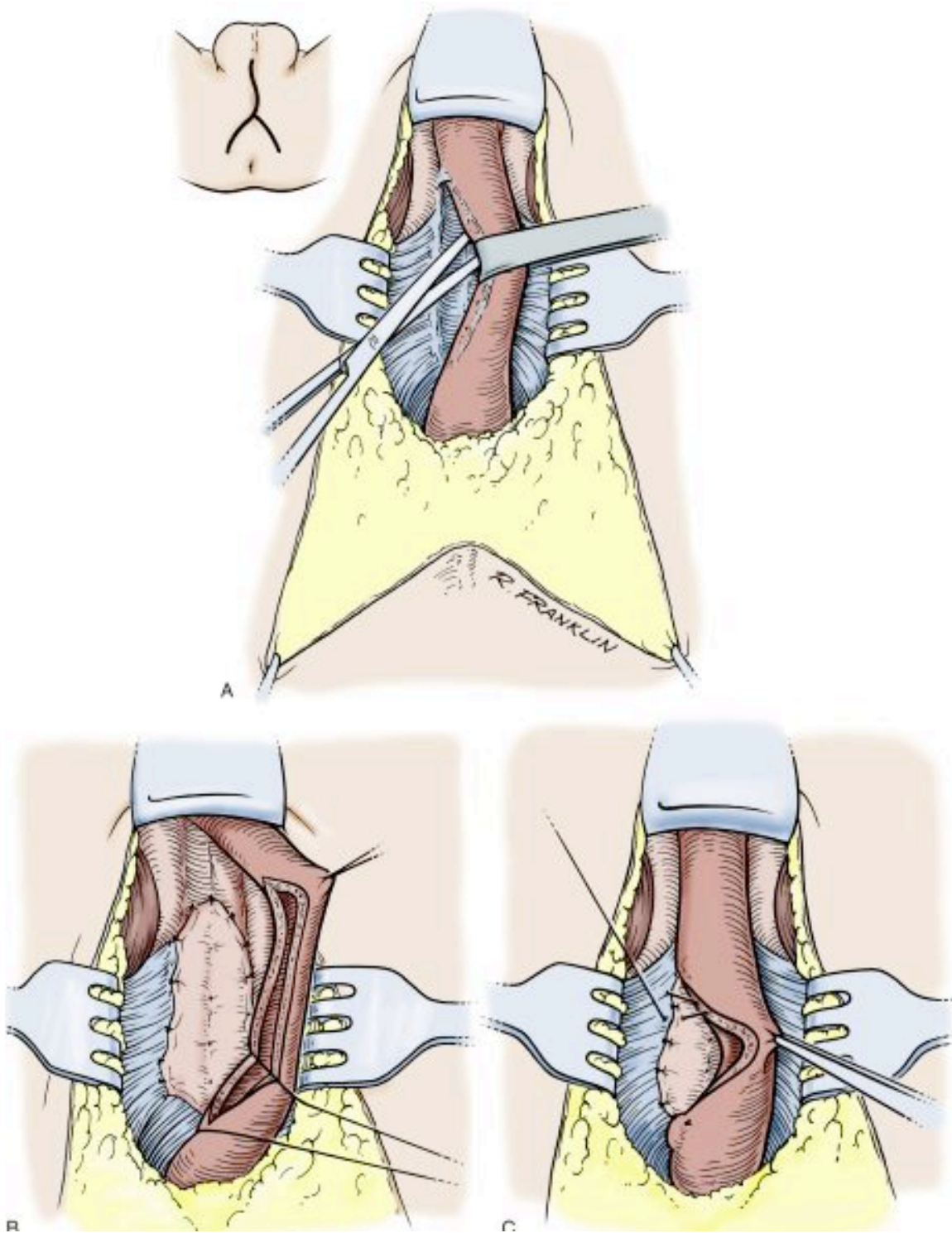
- 1yr later (some ppl wait only 3-4mo)
- proximal and distal portions of the urethra evaluated w/ bougies and cysto
- catheter passed into bladder
- 3cm wide strip marked to form new urethra, outlining flaps at each end to tailor junction of tube to existing urethra
- dissection carried out laterally to mobilize remaining skin
- approximate neo-urethral edges w/ interrupted sutures, w/ knots in lumen
- 2nd layer w/ running sub-epithelial monofilament to roll edges in
- skin closed
- suction drain
- SP tube



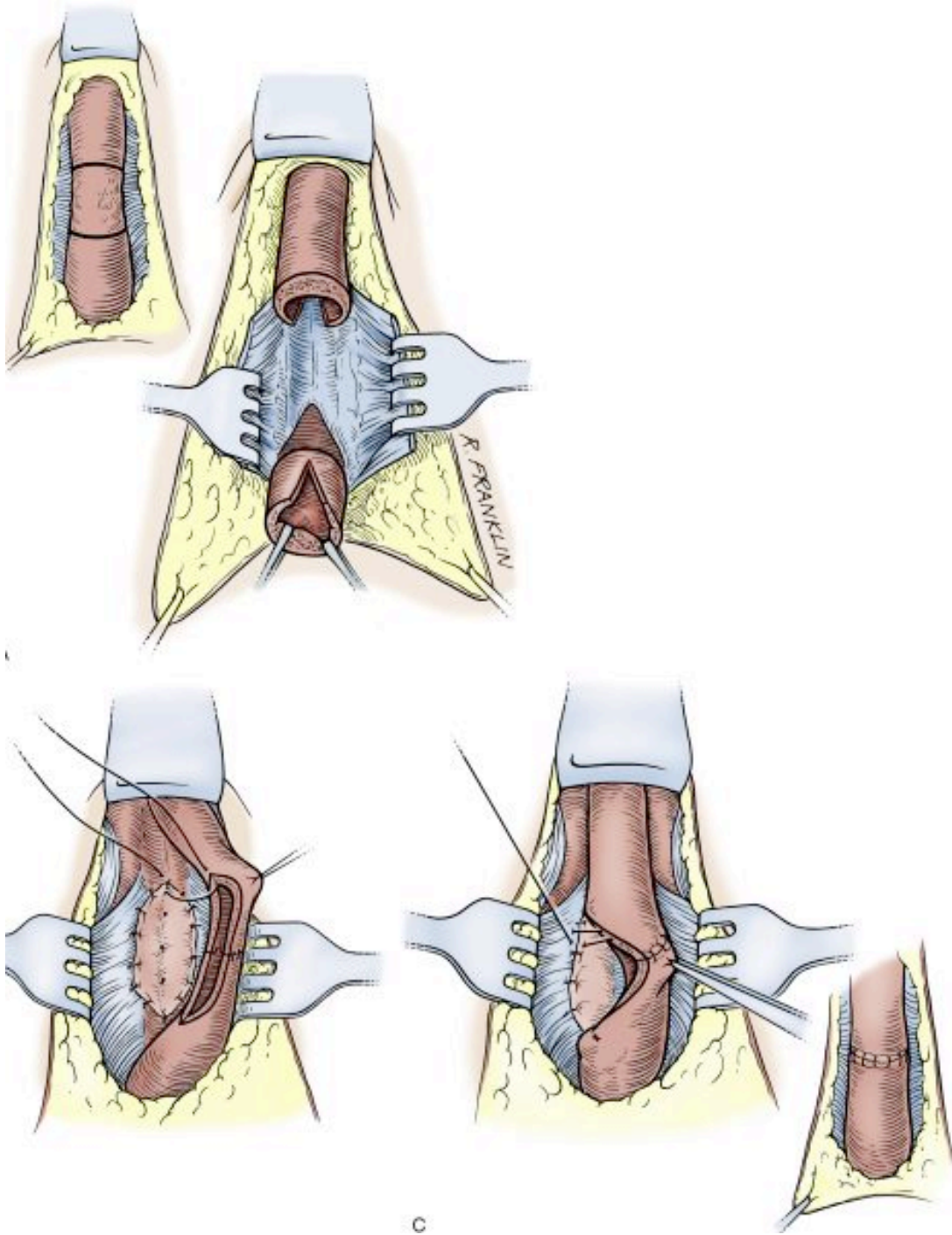
→ URETHROPLASTY } EXCISION + PRIMARY REANASTOMOSIS



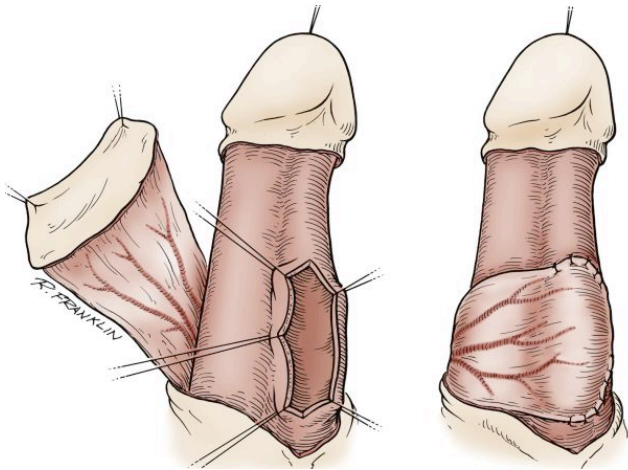
- URETHROPLASTY } INCISION + GRAFT ONLAY
- } A – VENTRAL ONLAY + SPONGIOPLASTY (worst option)
 - } B – LATERAL ONLAY (quilting to ischiocavernosus muscle)
 - } C – DORSAL ONLAY (BARBAGLI) (spread fixation of graft)



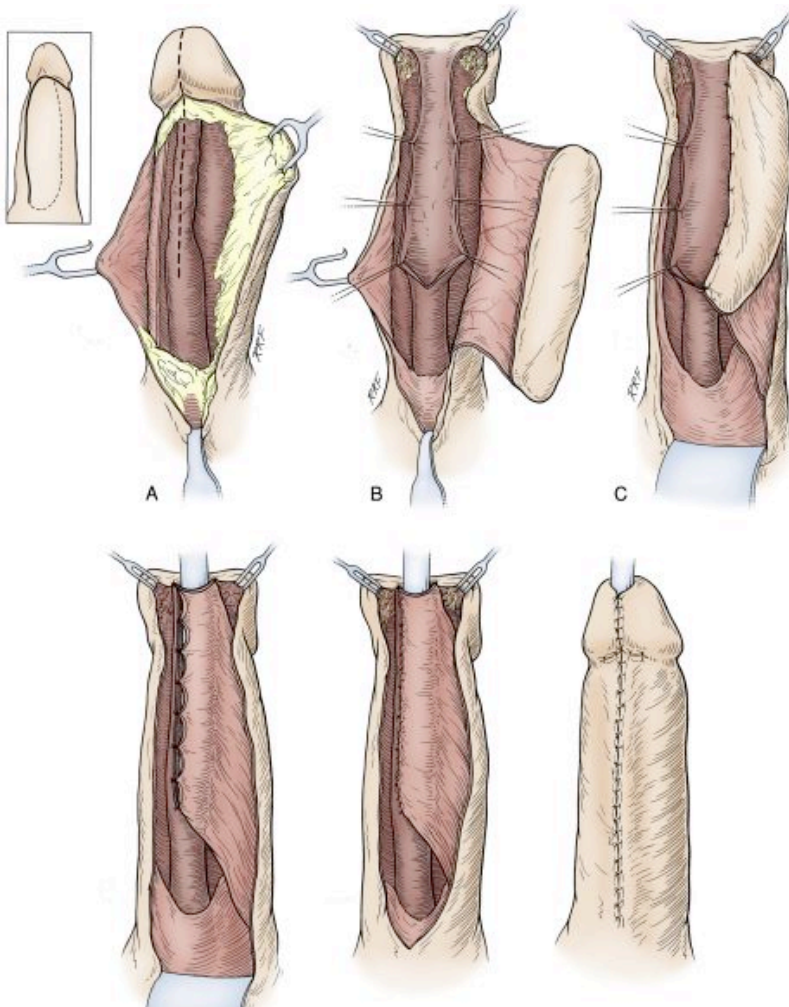
→ URETHROPLASTY } **INCISION + BARBAGLI DORSAL GRAFT ONLAY**



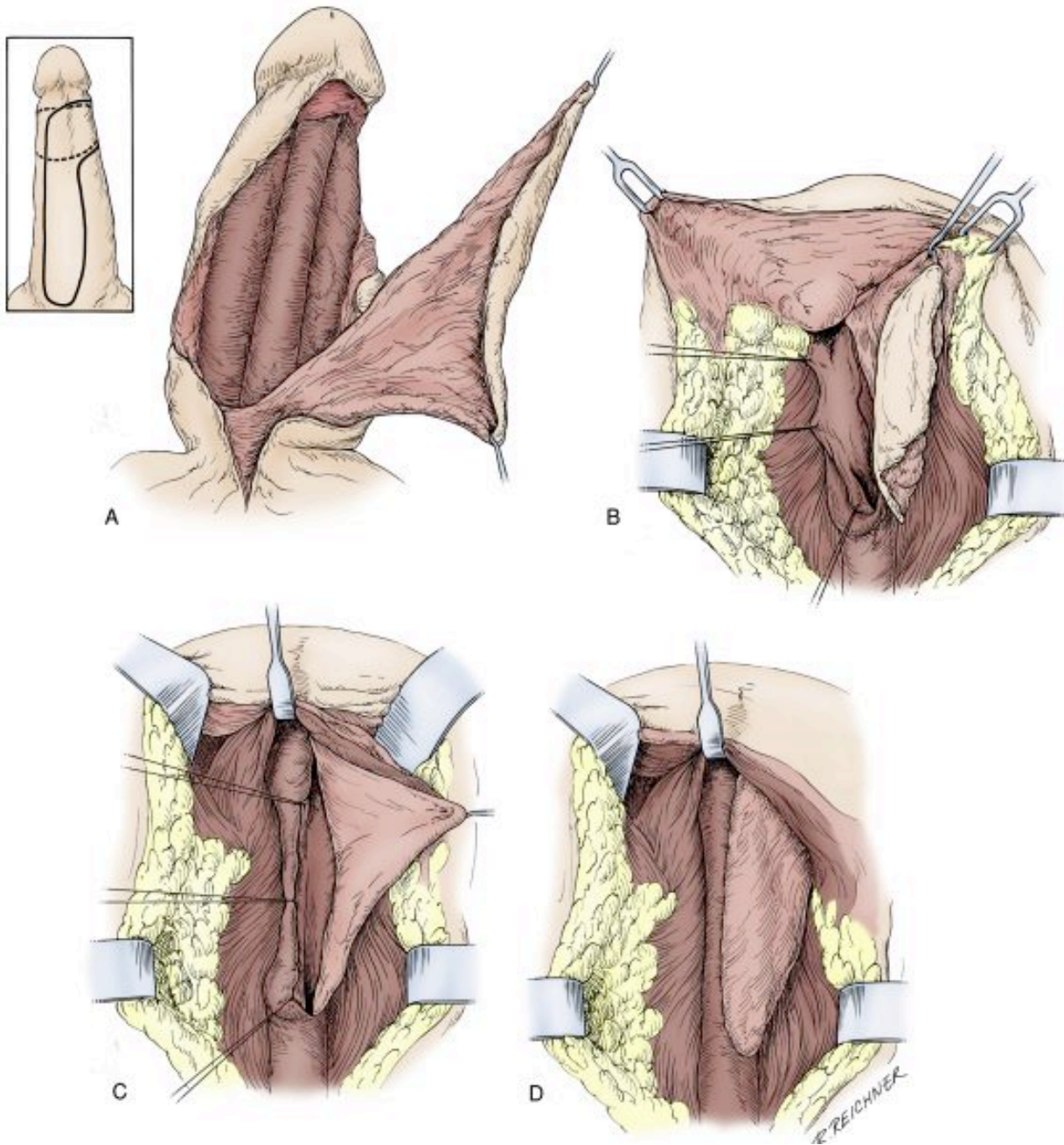
→ URETHROPLASTY } **EXCISION** + BARBAGLI DORSAL GRAFT ONLAY



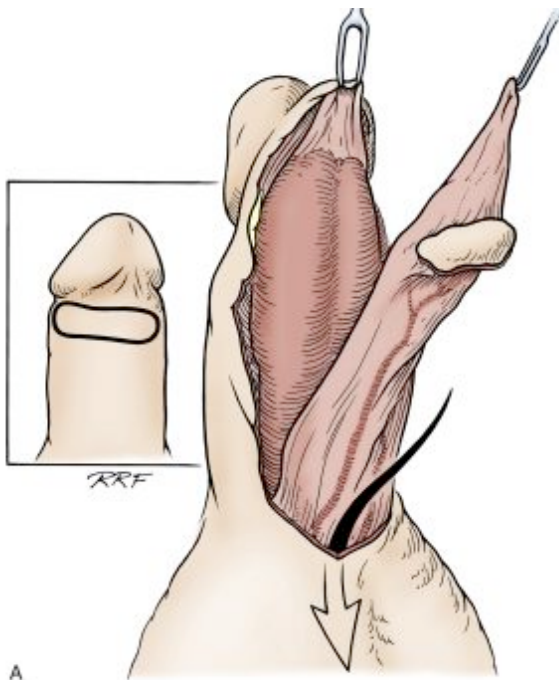
→ URETHROPLASTY } INCISION + FLAP RECONSTRUCTION
(dorsal transverse penile skin flap)



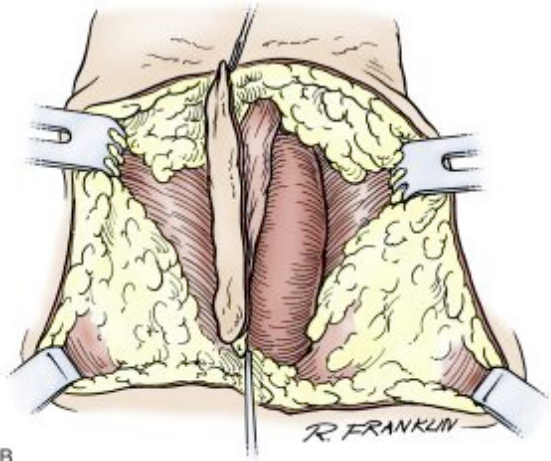
→ URETHROPLASTY } INCISION + FLAP RECONSTRUCTION
(ventral longitudinal penile skin flap)
 } distal stricture extending to meatus



→ URETHROPLASTY } INCISION + FLAP RECONSTRUCTION
 } **(ventral longitudinal penile skin flap)**
 } long bulbous stricture

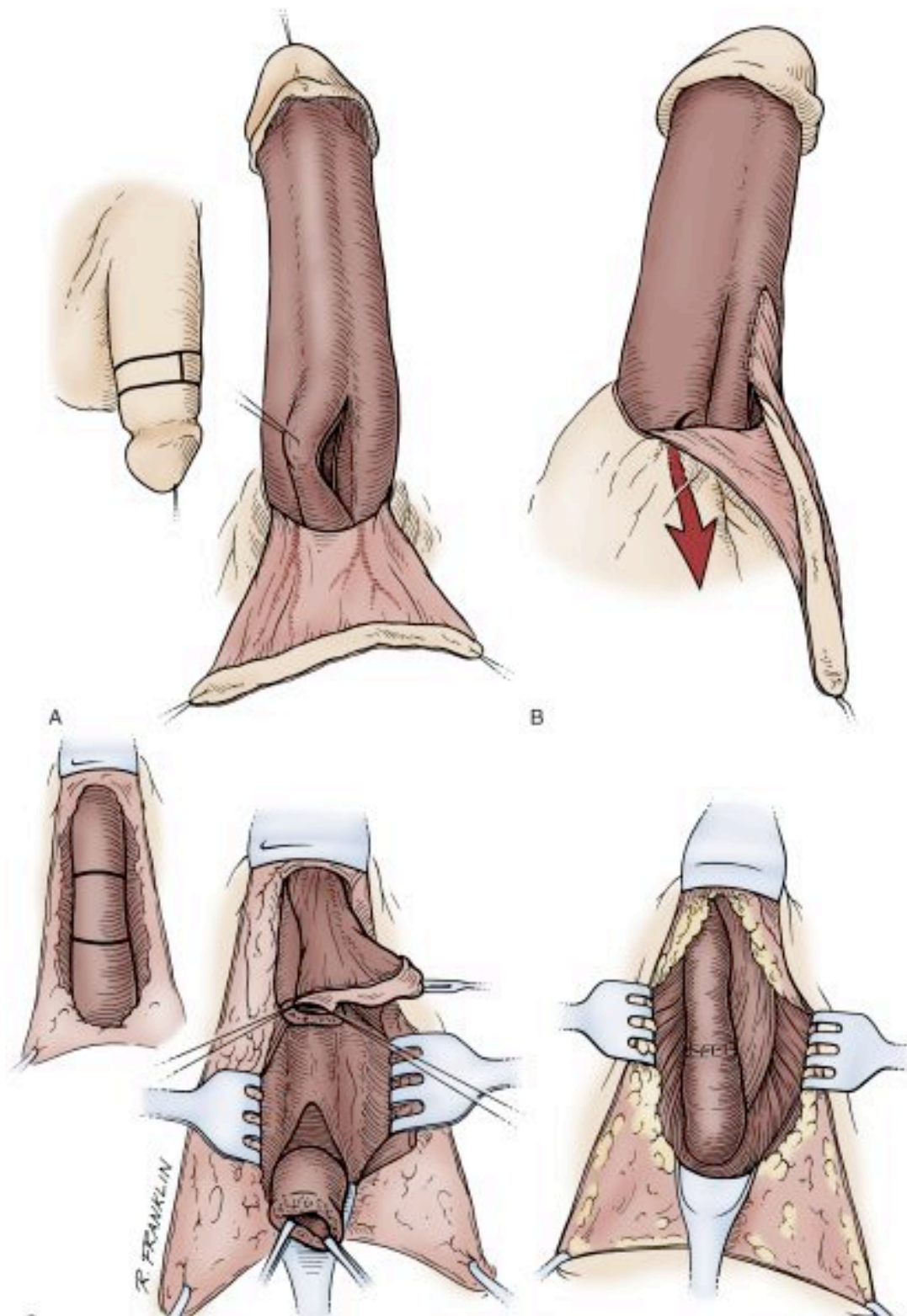


A



B

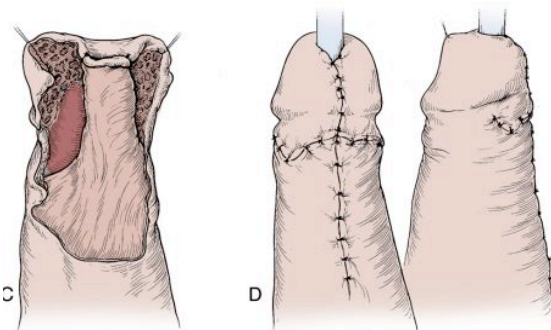
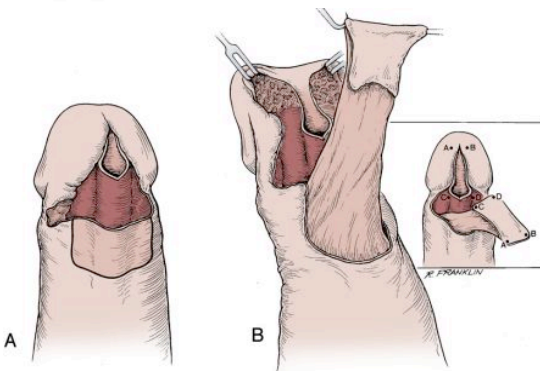
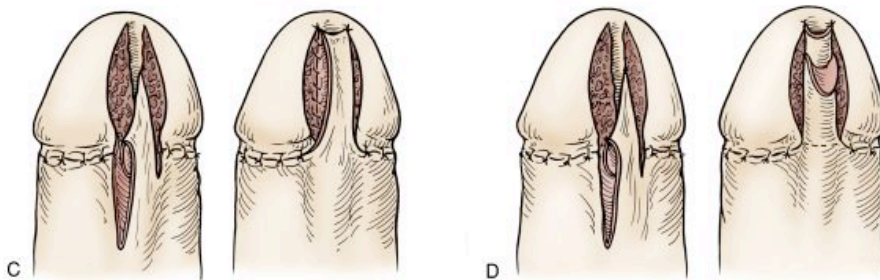
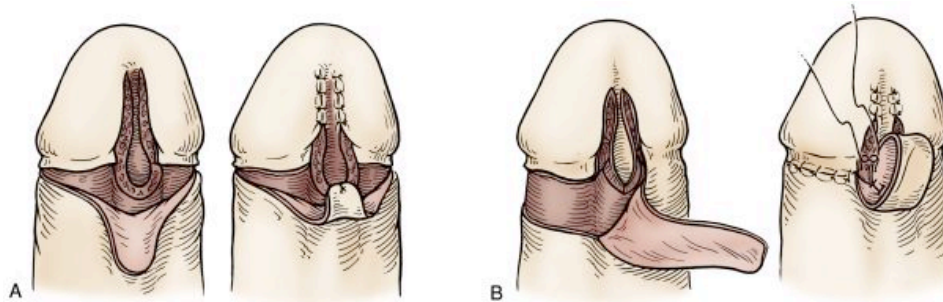
→ URETHROPLASTY } INCISION + FLAP RECONSTRUCTION
(ventral transverse penile skin)



→ URETHROPLASTY } EXCISION + FLAP RECONSTRUCTION (augmented anastomosis)
(ventral circular penile skin flap)

What are the different techniques used for reconstruction of the fossa navicularis?

- 1) dilation or meatotomy
- 2) spatulation of random penile skin flaps into meatotomy defect
 - often poor cosmesis
 - Blandy (small longitudinal flap), Cohney (transverse random flap), Brannen (midline random flap), DeSy (ventral longitudinal skin island w/ de-epithelialized portion), Devine (stenotic fossa excised and FTSG tabularized to replace fossa)
- 3) skin island flap elevated on dartos (Jordan)
 - split the glans



→ RECONSTRUCTION OF FOSSA NAVICULARIS STRICTURES

- BLANDY (1A) - COHNEY (1B)
- BRANNEN (1C) - DE SY (1D)
- JORDAN (2)

- 1) **endoscopic primary realignment } improves outcome of reconstruction**
- 2) excision + primary reanastomosis is goal } usually defects are short
 - **reconstruction is done at 4-6 months post-trauma if possible (DELAYED)**
 - may be limited by associated injuries (eg ortho)
 - associated injuries (eg urethrorectal fistula) can make reconstruction difficult
 - **most distraction injuries can be managed via a perineal approach**
 - Turner-Warwick popularized 1-stage perineal approach for short defects
 - Webster then made revision allowing for repair of long defects (up to 10cm)
 - usually can avoid transpubic or abdo-perineal approach (Waterhouse)
- 3) endoscopic management of PFUD injuries (eg cut-to-light)
 - has worse outcomes than open reconstruction and should be avoided
 - option reserved for those unfit for open sx (can't tolerate exaggerated lithotomy, etc)

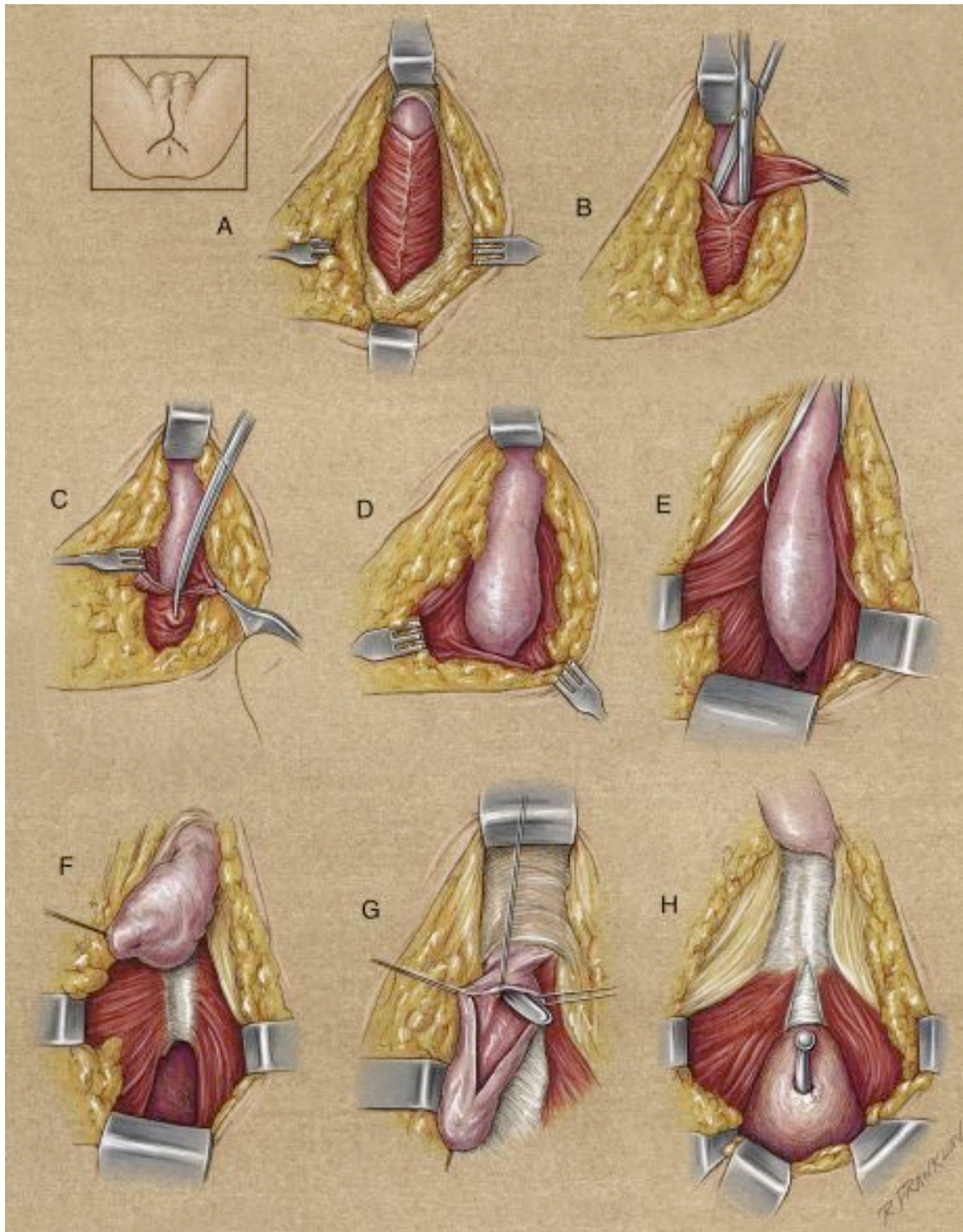
What are the main steps of perineal urethroplasty for PFUD injuries?

→ spatulated anastomosis of proximal anterior urethra to apical prostatic urethra

→ high rate of failure in pts w/ hypospadias & concomitant ant. urethral stricture

→ due to compromised distal retrograde flow

- position patient in exaggerated lithotomy } watch common peroneal nerve
- have retrograde and antegrade access (via S/P tube)
- λ incision w/ dissection anterior to transverse perineal muscles (ant. perineal triangle)
 - midline towards ischial tuberosities
 - Colles' fascia incised
- incise ischiocavernosus muscle until uninvested portion of corpus spongiosum is exposed
 - ischiocavernosus muscle must be dissected from corpus spongiosum and bulbospongiosum
 - length of bulb must be exposed
- self-retaining retractor placed
 - Scott, Jordan, etc
- mobilize corpus spongiosum off triangular ligament and corpora cavernosa
- detach bulbospongiosum from perineal body and open to expose bulb
 - monopolar cautery for proximal blood supply to bulbospongiosum (bulbourethral artery)
- divide triangular ligament and develop intracavernosal space down to pubis
 - ligate and divide dorsal vein if encountered
 - preserve dorsal or cavernosal arteries if encountered
- Haygrove staff passed antegradely and used to guide incision into posterior urethra
- resection of fibrosis until normal tissue planes
- retrograde cystoscopy to assess rest of posterior urethra
- primary reanastomosis when possible
 - mobilization of corpus spongiosum from attachments to corpora cavernosa if tension-free anastomosis not possible
 - detachment of Buck's fascia can improve mobilization, limiting the need for aggressive mobilization (can disrupt retrograde blood supply)
 - chordee may result after aggressive mobilization + primary reanastomosis
 - usually mild and doesn't affect sexual function
- spatulate proximal urethrotomy to ~32 Fr
- placement of anastomotic sutures (3-0 monocril)
- spatulate proximal end of anterior urethra to 30-32Fr
- final silastic Foley placed prior to tying down anastomotic sutures
 - copious irrigation of wound to reduce clot around area of anastomosis
- corpus spongiosum reattached to corpus cavernosa
- bulbospongiosum reattached to perineal body
- close ischiocavernosus muscles and Colles' fascia
 - JP drain placed deep to ischiocavernosus closure
- skin closed
 - JP drain placed in below subcutaneous closure, superficial to closure of Colles' fascia



→ PERINEAL URETHROPLASTY FOR PFUD (membranous urethral stricture)

What are the indications for immediate open primary realignment in PFUD injuries?

- 1) concomitant BN injury
 - 2) severe prostatomembranous dislocation (“pie-in-the-sky” bladder)
 - 3) concomitant rectal injury
- rarely indicated & assoc'd w/ high morbidity } recurrence of strictures (70%), ED (40%), SUI (20%)

What are the indications for open abdominal-perineal approach for repair of PFUD injuries?

- 1) concomitant urethrorectal fistula
- 2) concomitant vesicorectal fistula
- 3) skin or periurethral cavity requiring concomitant debridement and omentoplasty

What are the methods of gaining additional length for proximal urethroplasty?

- 1) **mobilization of corpus spongiosum from corpora cavernosa**
 - carried proximally to point of defect and distally as far as suspensory ligament
 - risk of chordee if mobilization carried distal to suspensory ligament
- 2) **separation of corporal bodies**
 - division of triangular ligament and development of intracavernosal space
- 3) **inferior pubectomy**
 - dorsal vein displaced laterally or ligated
 - gains additional 1-2cm
- 4) **corporal rerouting**
 - gains another 2cm
 - dissection must be performed away from surface of corporal bodies to avoid cavernous nerves
- 5) **total pubectomy**

What are the long-term sequelae of pubectomy associated with repair of PFUD injuries?

- shortening of penis
- destabilization of erection
- destabilization of pelvis
- chronic pain syndrome with movement/exercise

What is the post-op management after urethroplasty?

- Silastic urethral catheter
- urine diverted by S/P tube
- JP drain } removed according to drainage
- bed rest for 24-48hrs
- D/C with S/P tube, Foley, suppressive Abx
- pericatheter RUG and VCUG done at POD 3-4weeks
 - ensure no extravasation and that reanastomosis is widely patent
 - plug S/P tube and allow urethral voiding
 - can remove S/P after 5-7 days
- flexible cysto at 6months and 1yr, as well as prn based on voiding symptoms

What are the success rates of open urethroplasty for PFUD?

- **curative rates are 90-95% for primary reanastomosis**
- **~85% if tissue transfer technique used (graft or flap)**
- failures usually related to ischemia of proximal corpus spongiosum with ensuing stenosis of the mobilized corpus spongiosum
 - loss of antegrade blood flow into corpus spongiosum via bulbourethral artery
 - blood supply depends on retrograde blood flow via dorsal arteries through the glans
- risk of incontinence and ED likely due to initial injury not repair of PFUD

What are the RFs for bilateral deep internal pudendal artery injury at the time of trauma?

- evidence of injury to dorsal penile nerves
 - failed reconstruction at other centres
 - lateral impact pelvic fractures
 - “windswept” pelvic fractures
- \ / higher risk of
/ / ischemic atrophy

What is the role of duplex U/S in predicting reconstruction outcomes and ED?

- 1) **normal only if patient has normal pudendal arteries (unilateral or bilateral)**
 - if at least 1 pudendal artery intact, patients reliably cured + no ED
 - ➔ **no need for pudendal angiography if N duplex U/S**
- 2) **always abnormal if patient has only reconstituted arteries at best (unilateral or bilateral)**
 - if only reconstituted vessels, patients reliably cured BUT +ED
 - may benefit from corporal arterial revascularization
 - if not even reconstituted vessels, high chance of ischemia and failure of repair
 - will need corporal arterial revascularization BEFORE attempt at repair
 - ➔ **pudendal angiography indicated if duplex U/S abN**

VESICourethRAL DISTRACTION DEFECTS

What is the management of vesicourethral distraction defects?

- much more common now with increased number of RPs being performed
- can have totally obliterated distraction defect or severe anastomotic stenosis
- important to accurately determine length of defect
- 1) evaluation of defect
 - RUG
 - antegrade endoscopy via S/P tube
- 2) management of defect
 - indwelling S/P tube } especially in morbidly obese patients
 - cold knife incision at 3-o'clock and 9-o'clock
 - Holmium laser incision at 3-o'clock and 9-o'clock
 - incision + placement of UroLume + delayed placement of AUS
 - open reconstruction } when possible, preferred
 - } use combined abdominal-perineal approach
 - continent catheterizable bladder augmentation
 - urinary diversion

Outline the approach to open functional reconstruction of a vesicourethral distraction defect?

- mobilize bladder via lower midline incision and dissect along plane posterior to bladder
 - anterior bladder can be mobilized easier by incising an elliptical rim of superior pubic ramus (total pubectomy not required)
- perineal incision (posterior to transverse perinei muscles) used to develop plane anterior to rectal wall
- perineal dissection joined to abdominal dissection
- rectal wall completely peeled of area of fibrosis associated with distraction defect
- bladder opened and BN identified
- sound placed and advanced to area of obliteration
- completely resection of well-defined area of fibrosis
- urethral stump exposed and opened
- urethral stump anastomosed to marsupialized neobladder neck
- catheter placed before completely tying down anastomosis
 - balloon not always inflated
 - can be held in place via suture to abdo wall button
- omentum mobilized and placed between posterior wall of anastomosis and anterior rectal wall
- omentum then wrapped around area of anastomosis
 - if tension on anastomosis can use Vest sutures (suture passed out perineum)
- JP drain placed in lateral vesical spaces
- S/P tube left in situ and vesicostomy closed
- post-op care same as for RP

COMPLEX FISTULAS OF THE POSTERIOR URETHRA

What are the management options for complex fistulae of the posterior urethra?

- most fistulae of the posterior urethra are small
 - can be managed by a transperineal, transanal-transsphincteric, or posterior approach
- complex fistulae, especially if assoc'd w/ RADs or large granulated cavities, require unique approaches
- functional reconstruction when possible
- 1) open functional reconstruction (similar to approach for vesicourethral distraction defects)
 - see description of combined abdo-perineal approach above
 - omental wrap even more important
 - can also use rectus abdominis muscle flap or peritoneal urachal flap
- 2) BN closed off + continent catheterizable bladder augmentation
 - omentum, rectus abdominis muscle flap, or peritoneal urachal flap used to bolster closed BN
 - consider defunctioning bowel if high risk (eg radiation)
- 3) diversion with ileal conduit or bowel pouch } especially for radiation cases

CURVATURES OF THE PENIS

What are the causes of chordee?

→ chordee refers to the curvature not the lesion

- 1) congenital
 - true congenital curvatures } dorsal, lateral, ventral
 - } associated with hypercompliance of tunica albuginea
 - **usually large penis when erect**
 - } if lateral, usually to left
 - } dorsal not common
 - “chordee without hypospadias” } normally placed meatus but ventral chordee due to inappropriate fetal development of ventral penile structures
 - } erect penis is commensurate w/ size of flaccid penis

→ even if corpus spongiosum abN, ventral limiting factor is NOT corpus spongiosum

→ penis curved usually due to inelasticity of ventral aspect of corpora cavernosa
- 2) acquired
 - usually no curvature before puberty (sexually active)
 - intercourse-related } usually lateral
 - Peyronie's disease } often have ED and penile shortening
 - iatrogenic (eg post-VIU)

What is the Devine-Horton classification of congenital chordee?

- type I } meatus at tip of glans but none of surrounding layers are normally formed
 - } corpus spongiosum NOT normally fused
- type II } fibrous band derived from mesenchyme lies ventrolateral to urethra
 - } meatus at tip of glans and normal corpus spongiosum
- type III } short area of inelastic tissue in dartos layer of penis
 - } meatus at tip of glans and normal corpus spongiosum

→ **type I, II, III are considered “chordee without hypospadias”**
- type IV } relative shortness or inelasticity of one aspect of tunica albuginea
 - } associated with hypercompliance of tunica albuginea (large penis erect)

→ **congenital chordee**
- type V } aka congenital short urethra (very rare)
 - } normal fusion of all layers but urethra and corpus spongiosum not compliant enough compared to other ventral tissue layers

What are the surgical management options for “chordee without hypospadias”?

- 1) mobilization and excision of dysgenetic tissues
- 2) mobilization of corpus spongiosum (from glans into perineum)
- 3) kids } longitudinal incision in ventral midline of corpora cavernosa
 } can also mobilize dorsal NVB with Buck's and excise a small ellipse from dorsal tunical albuginea (plication)
- 4) elliptical incisions on side of curvature + autologous graft

What are the surgical management options for **CONGENITAL** chordee?

- 1) **Nesbitt type repair**
 - excision of ellipses of tunica albuginea directly opposite point of maximal concavity with corporal plication
 - **PREFERRED OPTION BECAUSE LENGTH NOT AN ISSUE FOR CONGENITAL CHORDEE**
 - **WHO 2002 } majority or all patients should have plication procedure**
 } can get graft-induced veno-occlusive dysfunction
- 2) lengthening of ventral aspect
 - placement of autologous tissue or SIS grafts after making transverse incisions into ventral tunica albuginea
- 3) corporoplasty (described by Yachia)
 - longitudinal incisions in tunica albuginea with transverse closure

What are the surgical management options for **ACQUIRED** chordee?

- differentiate from Peyronie's disease, which often has ED and penile shortening
- patients don't like indentation and curvature
- likely from subclinical fractures
- 1) Nesbitt type repair
- 2) **lengthening of ventral aspect**
 - use of autologous tissue or SIS grafts
 - **PREFERRED OPTION BECAUSE BETTER COSMESIS AND FUNCTIONALITY**

TOTAL PENILE RECONSTRUCTION

What flaps can be used for total penile reconstruction?

1) forearm flap

→ **most commonly used method for total penile reconstruction**

→ **fasciocutaneous flap vascularized by the radial artery**

→ elevated and transferred on the superficial fascia

a) Chang "Chinese" flap

- skin island has 2 separate paddles:

→ ulnar "urethral" paddle

→ shaft covered by radial aspect of skin paddle

- 2 islands separated by de-epithelialized strip

- urethral tube rolled within the tube of skin to form a tube-within-a-tube

- **tends to lead to ischemic stenosis of the urethral paddle**

b) Cricket bat modification

- centers urethral portion over radial or ulnar artery

- urethral tube extends distally

- proximally, broader skin paddle forms shaft coverage

- **useful in trauma pts with a decent stump of erectile tissue and urethra**

c) Biemer modification

- centers urethral paddle over radial artery

- includes portion of **radius bone to give rigidity to penis**

- urethral paddle is a midline strip between 2 lateral skin paddles (to cover shaft) separated by 2 de-epithelialized strips

→ **best cosmetic result when combined with Puckett glanular reconstruction design**

d) Puckett modification

- similar to Biemer modification

- large island left distally, flared back over tip of the tubed flaps, creating illusion of glans

2) upper lateral arm flap

→ **if you need only vascularized tissue to cover penile shaft**

→ **based on radial collateral artery**

→ fasciocutaneous flap

→ scar more easily hidden

What are the disadvantages to the use of a forearm flap for phallic reconstruction?

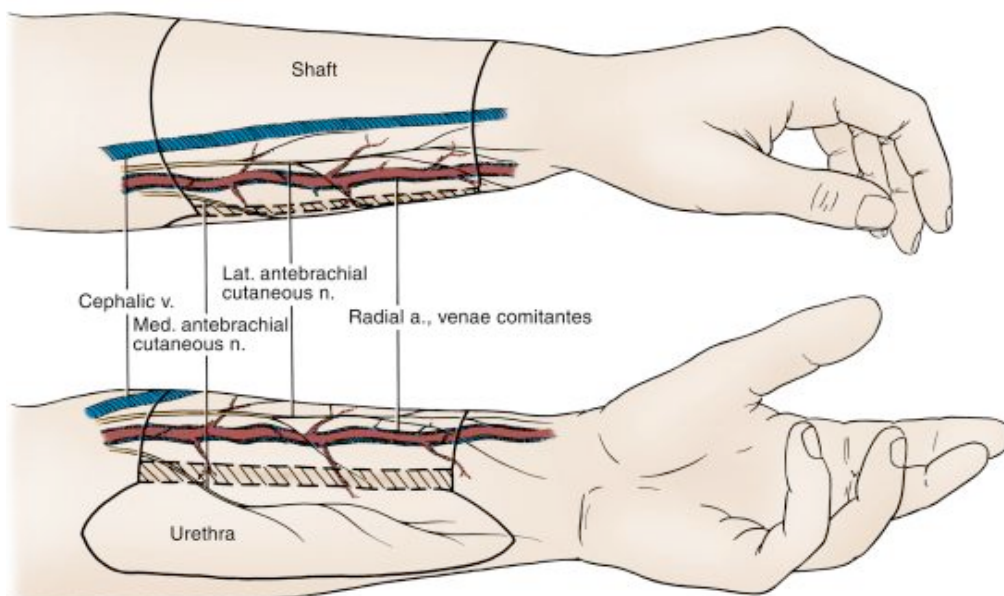
- donor site deformity } scar
 - can reconstruct w/ FTSG from groin crease
- cold intolerance to donor hand
- hirsute forearm skin } hair in urethra

What recipient vasculature can be used for flap transfer?

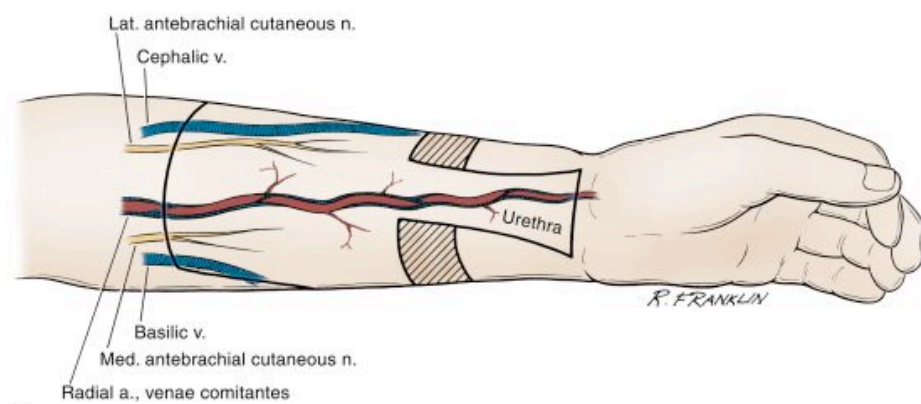
- deep inferior epigastric vessels
- saphenous interposition graft to superficial femoral artery

What principles should be followed for penile reconstruction after trauma?

- urinary diversion
- debride necrotic tissue
- remove any foreign bodies
- save as many penile structures as possible
- primary reconstruction 3-6 weeks after trauma (some wait 4-6 mo)
- imperative that well-vascularized tissues be eventually transposed to adjacent area and reconstruction of these areas can be accomplished with a number of flaps

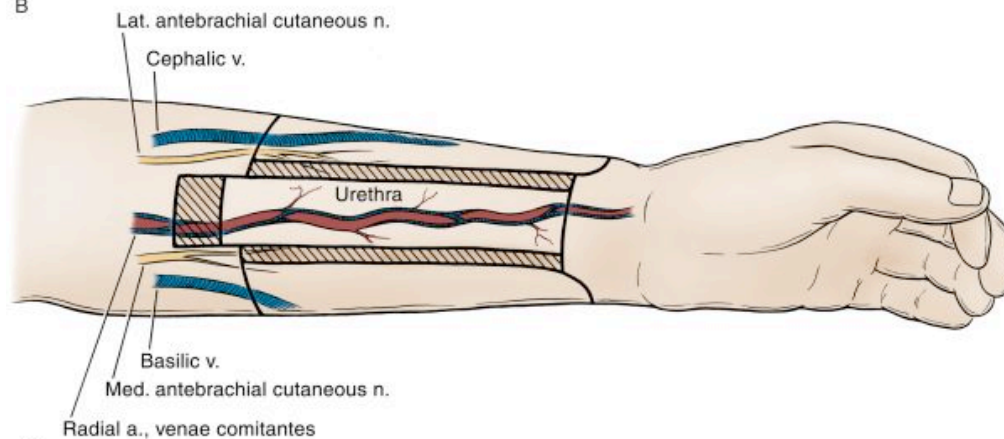


RBR
A



R. FRANKLIN

B



C

→ FOREARM FLAP FOR TOTAL PENILE RECONSTRUCTION

A – CHANG “CHINESE”

B – “CRICKET BAT”

C - BIEMER

What other flaps have been used to reconstruct the penis after trauma?

- 1) Tensor fascia lata (TFL) flap
→ for groin reconstruction
- 2) rectus femoris flap
→ for inguinal and lower abdominal reconstruction
- 3) gracilis muscle
→ for perineum and groin
- 4) posterior thigh flap
→ for perineum and groin
- 5) rectus abdominis flap

FEMALE-TO-MALE TRANSSEXUALISM

What is the management of the female-to-male transsexual patient?

- complex screening and evaluation by mental health professionals, surgeons
- 1st stage
 - BSO+TAH, vaginectomy, urethral lengthening w/ colpocleisis
 - divert urine x 3 weeks
- 2nd stage
 - 3-4 months later
 - penile reconstruction
- 3rd stage
 - 1yr later
 - if urethra durable and erogenous sensibility demonstrated then prosthetic implant can be considered

Chapter #34 – Scrotal & SV Surgery

SCROTUM

What does the midline raphe represent?

- runs from meatus to anus and represents **fusion of genital tubercles**

What are the layers of the scrotum?

- skin → pigmented, hair bearing, devoid of fat, rich in sebaceous glands
- dartos → continuous with dartos of penis, Colles' in perineum and Scarpa's in abdomen
- external spermatic fascia → from external oblique fascia
- cremaster muscle and fascia → from internal oblique muscle
- internal spermatic fascia → from transversalis fascia
- tunica vaginalis → from peritoneum

What is the blood supply to the scrotum?

- anterior } deep external pudendal vessels (branch of femoral vessels)
 } don't cross midline raphe
- posterior } posterior scrotal branch of perineal vessels (branch of internal pudendal)

What is the innervation of the scrotum?

- anterior } ilioinguinal (L1) and genitofemoral (L1-L2) nerves
 } don't cross midline raphe
- posterior } posterior scrotal branch of perineal nerve (from pudendal nerve)

What is the blood supply to the testis?

- testicular artery } from aorta
- deferential artery } from inferior vesical artery (branch of internal iliac)
- cremasteric artery } from inferior epigastric artery

What is the blood supply to the epididymis?

- superior epididymal artery } from testicular artery
- inferior epididymal artery } from deferential artery

What is the blood supply to the vas deferens?

- deferential artery (SV end)
- inferior epididymal + deferential artery (testis end)

Vasectomy

What are the different methods of performing a vasectomy?

- ~5% will seek reversal
- open vasectomy (midline incision vs bilateral incision)
- no-scalpel vasectomy
- percutaneous vasectomy
- high-frequency U/S vasectomy
- laparoscopic (combined with intra-abdo surgery eg hernia repair)

What are the advantages & disadvantages of the different approaches to vasectomy?

	ADVANTAGES	DISADVANTAGES
midline	- one incision	- small chance of dividing same side twice
bilateral	- less chance of dividing same side twice - can ligate vas far from testicle	- 2 incisions

What are the important peri-op issues to discuss with the patient?

- document counseling
- confirm vasal tissue in vasectomy specimen
- f/u semen analysis documenting azoospermia

Describe the main points of a vasectomy?

- isolate vas from spermatic cord vessels and bring to skin
- local anesthetic injected into skin and within perivasal sheath
- vas delivered into incision
- deferential artery, veins, and accompanying nerves are dissected free of vas and spared
- segment of vas removed
- ends are clipped or tied +/- cauterized +/- intraluminal cautery
- hemostasis + close

What are the benefits of the no-scalpel vasectomy?

- smaller wound
- less infections
- faster
- fewer hematomas
- less pain

What are the potential complications following vasectomy?

→ less common with no-scalpel technique

→ early

- hematoma (most common – 2%)
- infection
- injury to vas, testis, epididymis
- sperm granuloma } higher risk of recanalization (likely develops in all men eventually)
 - } presence associated with less epididymal & testicular damage
 - } predicts higher likelihood of VV success

→ long-term

- chronic testicular or epididymal pain } 1 in 1000
- altered testicular function
- testicular atrophy (cord injury)
- chronic epididymal obstruction
- anti-sperm Ab's } detectable levels found in 60-80%
- failed vasectomy (recanalization - <1%) } any motile sperm at 3 months
- vasitis nodosa (just a histologic dx, no pathology)
- ?Pca risk } likely a detection/referral bias

What methods are used to reduce the likelihood of recanalization (CHART)?

- suture ligation } 1-5% failure rate
- metal clips on each end } <1% failure rate
- intraluminal cauterization of vas with needle-point cautery } <0.5% failure rate
- closing dartos fascia over one end of cut vas (**fascial interposition**) } **BEST METHOD**

→ failure after vasectomy invariably associated with sperm granuloma formation

→ open-ended vasectomy lowers chance of post-vasectomy pain but failure rates higher d.t. recanalization

What is the significance of “rare non-motile sperm” on post-vasectomy semen analysis?

- these men ultimately become azoospermic } contraception is cautiously discontinued

→ motile sperm at 3 months = failure

How common are spermatoceles?

- What are the indications for treatment of a spermatocele?

- ## What are the potential complications after spermatocelectomy?

- ### What are the etiologies of epididymal tumours?

- open surgical
 - NB – use inguinal incision if any abn'ty of testis on pre-op P/E or scrotal U/S
 - hydrocele sec delivered intact when possible and opened in avascular plane anteriorly, away from testis, epididymis, vas, and cord structures
 - large hydroceles can significantly distort normal anatomy
 - +/- hydrocele fluid for culture or cytology
 - 1) Jaboulay } less chance of recurrence but higher chance of complications
(more dissection and bottleneaking around cord structures)
 - 2) Lord's } fast and less complications but not for multiloculated hydroceles or thick-walled hydroceles due to large bundle of residual tissue
- sclerotherapy
 - mainly useful for older men in whom fertility is not an issue
 - local anesthetic
 - tetracycline (small risk of epididymal obstruction)
 - alcohol (small risk of epididymal obstruction)

What are the potential complications after hydrocelectomy?

- hematoma/bleeding
- infections
- injury to the vas
- injury to the epididymis
- testicular atrophy
- recurrence

Testicular surgery

What is the DDX of chronic testicular pain?

- 1) chronic orchialgia
 - intermittent or constant scrotal pain (unilateral, bilateral, or alternating) lasting >3mos
 - Rx → Doppler U/S
 - treat underlying cause
- 2) chronic epididymitis
 - usually have +ve semen or urine cultures } rule out urethral stricture
 - if fertility is an issue, DO NOT perform diagnostic puncture
 - Rx → Abx +/- anti-inflammatories, sitz baths
 - if refractory, consider epididymectomy
- 3) varicoceles
 - usually only large varicoceles cause symptoms
 - symptoms usually resolve in supine position
 - Rx → varicocelectomy for refractory symptoms or infertility
- 4) post-hernia repair orchialgia
 - likely nerve entrapment injury
 - Rx → most resolve with conservative therapy
 - if refractory, consider exploration + removal of nonabsorbable sutures, neurolysis
- 5) post-vasectomy pain syndrome
 - difficult to treat (1 in 1000) } chronic epididymal congestion, sperm granuloma
 - Rx → minimum 3 month trial of NSAIDs, sitz baths, etc
 - if refractory, consider cord blocks, vas reversal, epididymectomy or excision of sperm granuloma + intraluminal cautery
- 6) chronic intermittent torsion

What is the management of chronic orchialgia NYD?

- must r/o non-scrotal etiologies } LUTS, distal ureteric stone, occult hernia, IBS
- Rx → conservative therapy (NSAIDs, sitz baths, etc) for 3-6 months
- denervation surgery } goal is to transect all nerve fibers from genitofemoral nerve
 - some advocate preservation of vas
 - transecting vas may also eliminate sympathetics innervating testis
- } preservation of vasal vessels + testicular artery + lymphatics +/- vas

What is the recommended management of UDT in adults?

- 1) unilateral + normal contralateral testis = likely fertile
 - orchidopexy if unable to monitor } for Ca risk and to increase hormonal function
 - orchiectomy if fertility not an issue } NOT NECESSARY IF >50yrs (Oh, et al '02)
- 2) bilateral UDT = usually azoospermic
 - bilateral orchiopexy recommended for most } can induce spermatogenesis and also preserves hormonal function

What is the management of persistent retractile testes in adults?

- some will be infertile } resembles semen parameters like varicocele (OAT)
- bilateral orchidopexy may improve semen quality and fertility
- should perform dartos pouch operation

Varicocelelectomy

What are the indications to perform a varicocelelectomy?

- 1) infertile male with:
 - a) normal female partner or potentially treatable cause of infertility
 - b) clinical varicoceleAND
 - c) abnormal S/A
- 2) male with clinical varicocele, abnormal S/A, and plans for future conception
- 3) adolescent male with clinical varicocele and reduction in size of ipsilateral testis
- 4) chronic orchialgia not attributable to another cause
- 5) ?cosmesis

What are the different approaches to varicocelelectomy?

- 1) scrotal approach
 - historical approach } high risk of injury to testicular artery + high rate of failure due to complex pampiniform plexus
- 2) retroperitoneal approach
 - ligation of internal spermatic vein as it exits inguinal canal w/ preservation of internal spermatic artery
 - transverse abdo incision at level of internal inguinal ring, 2 fingerbreadths medial to ASIS
 - enter retroperitoneum and reflect peritoneum medially to expose internal spermatic vessels
 - **recurrence is common (15%)**
- 3) lap approach
 - same as retroperitoneal approach
 - rarely used in adults due to invasiveness and risk of ligating testicular artery
 - incise peritoneum just lateral to spermatic cord and dissect out and ligate testicular vein
 - some advocate ligation of all spermatic vessels because testis has other arterial supply
 - recurrence rate <2%
 - hydrocele in 5%
- 4) inguinal approach
 - 1-4cm oblique incision made just above ext inguinal ring
 - open ext oblique aponeurosis } watch out for ilioinguinal nerve
 - ligate dilated veins (2-0 silk or clips) but preserve lymphatics + arteries
 - ligate any external cremasteric veins also
- 5) subinguinal approach
 - 2-3cm transverse incision made over ext inguinal ring
 - identify cord as it exits external ring
 - ligate dilated veins including cremasterics
 - less morbidity but more difficult due to increased # of branches
- 6) transvenous embolization/sclerosis

SEMINAL VESICLES

What are the embryologic origins of the SVs?

- strictly male organ } no female homolog
- develops from 2 buds from **distal mesonephric duct** at ~12 wks gestation
 - renal anomalies usually associated with SV anomalies

What is the most common location of insertion of ectopic ureters in males?

- **posterior urethra/bladder neck (~50%)**
- SV (30%)
- prostatic utricle (10%)
- vas or ejaculatory duct (10%)

What is the function of the SV?

- motility & metabolism of sperm (fructose) + coagulation of semen (semenogelin)
- **SV fluid contributes ~50-80% to ejaculate volume**
 - average volume of 2.5mL
 - pH is slightly **alkaline**
- SV fluid contains mainly fructose (sperm motility) and PGs (E, A, B, F)
 - also has **semenogelin 1** (sperm motility inhibitor – cleaved by PSA after ejaculation)

What are the normal anatomic parameters of an SV?

- 5-10cm long, 3-5cm wide } size decreases with age
- most commonly has 1 central canal with only a few side branches
- **luminal diameter >1.5cm = dilated system**

What is the blood supply to the vas and SV?

- **vesiculodeferential artery** → br. of superior vesical (br. of internal iliac)
- may get more blood supply from inferior vesical artery (also a br of internal iliac)
- both drain into the **pelvic venous plexus**

What is the lymphatic drainage of the SV?

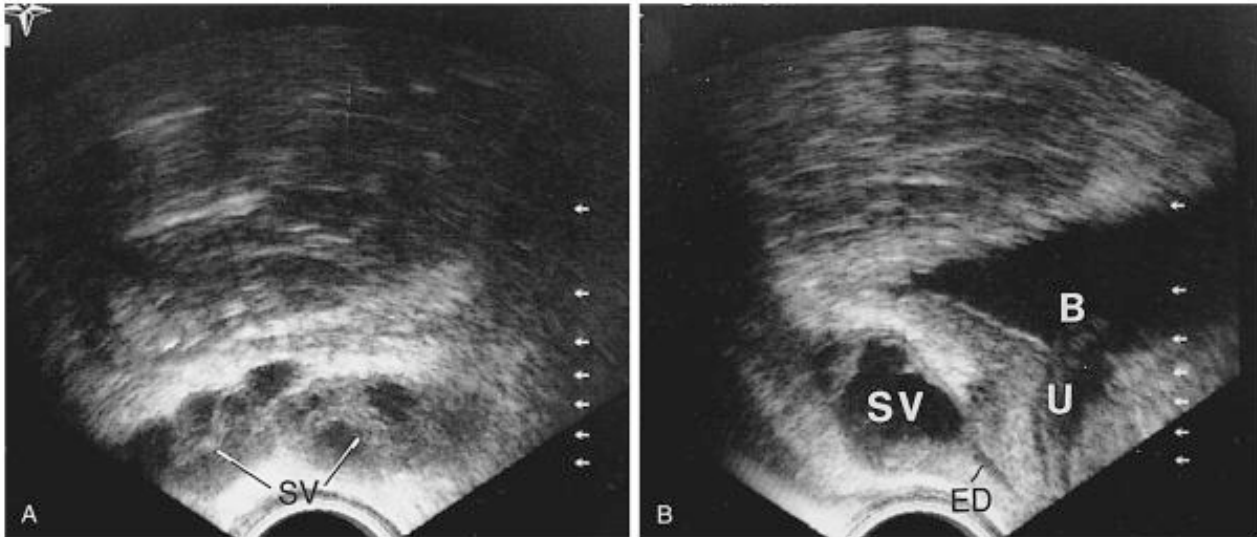
- external & internal iliac nodes

What is the innervation of the SV?

- mostly from the **pelvic autonomic plexus**
- mainly excitatory sympathetics from hypogastric nerves } ejaculation is sympathetic

What tests are used to work-up possible SV pathology?

- P/E } usually non-palpable
- semen analysis } low volume, no fructose, acidic pH, lack of liquefaction may imply pathology of SV (absence or ED obstruction)
- TRUS } normally elongated and flat between rectum and bladder just superior to prostate
 - } predominantly symmetrical with hypoechoic center
 - } abN findings include SV aplasia, atrophy, obstruction, and cysts
- CT or MRI } mainly for staging
 - } also to r/o other anomalies



→ NORMAL TRUS OF SEMINAL VESICLES

What are the parameters on TRUS that are consistent with obstruction?

- >1.5cm diameter
- >3.5cm long
- large anechoic areas containing sperm on aspiration (≥ 4 motile sperm/HPF)

What are the imaging features of SV tumours?

- can't differentiate benign from malignant } both are **hyperechoic relative to N SV**
- CT and MRI no better than U/S at differentiating
- primary } usually unilateral
- } usually not contiguous
- secondary } usually bilateral
- } often difficult to distinguish origin of tumour

What is the DDx of SV calcification?

- **DM (most common)**
- TB
- schistosomiasis
- old bacterial abscess

Pathology

What conditions are associated with UNILATERAL agenesis of the SV?

- occurs in ~1%
- 1) ipsilateral absence of vas
- 2) **ipsilateral renal anomalies } found in 80-90%**

What conditions are associated with BILATERAL absence of SV?

- 1) congenital bilateral absence of vas (CBAVD) } 70-80% have CF gene mutation
- if associated w/ GU anomalies, CF is rare
- } 80-90% with CF have CBAVD

What are the common causes of chronic seminal vesiculitis?

- 1) ectopic ureter
- 2) bacterial prostatitis

What are the RFs for SV abscesses?

→ MRI best test if suspected } low intensity on T1, very high intensity on T2

- 1) DM
- 2) chronic indwelling catheter
- 3) endoscopic manipulation

What are the causes of SV tumours?

1) **benign (most common)**

- papillary adenoma } usually unilateral
- cystadenoma } usually unilateral
- amyloid } more common with increasing age
- fibroma
- leiomyoma
- simple cysts } often associated with ectopic ureter, renal agenesis, PCKD
- hydatid cyst (ecchinococcus)

Rx → periodic follow-up, unless symptomatic, then simple SVectomy

2) **malignant**

- primary } adenocarcinoma
- } sarcoma
- } cystosarcoma phyllodes
- } seminoma
- } carcinoid

Rx → radical excision (cystoprostatectomy + PLND) OR pelvic exenteration

→ +/- adjuvant Rads

- secondary } bladder, prostate, lymphoma, rectal invasion

What are the features of primary adenocarcinoma of the SV?

- rare } usually in men >50yrs old
- usually extends locally } common to see prostatic or ureteral obstruction
- **mucin-producing papillary or anaplastic carcinoma**
- **CEA is elevated (normal PSA)**
- stains **+ve for CA-125**

Rx → radical excision

What are the features of primary SV sarcoma?

- very rare
- no distinguishing features } diagnosed on Bx
- leiomyosarcoma, mullerian adenosarcoma-like tumour
- aggressive behaviour

Rx → radical excision

What are the causes of SV cysts?

→ congenital } often associated with **ipsilateral ectopic ureter or renal agenesis or PCKD**

→ acquired } due to obstruction (eg post-TURP)

How do patients with SV cysts usually present?

→ most are asymptomatic

- can present with some symptoms } dysuria
- } painful ejaculation
 - } hematospermia
 - } recurrent epididymitis
 - } infertility

What are the main indications for SV surgery?

- 1) congenital cysts with infection or obstruction, causing infertility
→ aspiration or transurethral unroofing
- 2) ureteral ectopy into SV with resultant renal dysplasia or obstruction
- 3) primary tumours
- 4) chronic seminal vesiculitis, refractory to meds

What are the different approaches to seminal vesiculectomy?

- transperineal } minimally invasive but higher risk of ED
 } not recommended for congenital lesions
 → can't address commonly associated renal anomalies
- transvesical (incision through posterior bladder wall) } more blood loss and higher risk of ureteral injury
 } rectal injury less common
- paravesical } for kids with unilateral cyst and when nephroU is required
- retrovesical } for bilateral excision
- transcoccygeal } if hx of multiple suprapubic or perineal surgeries
- laparoscopic or robotic } usually less blood loss and excellent visualization
 } risk of bladder injury, rectal injury, ureteric injury, ED

What are the different management options for SV cysts or abscesses?

- TUR
- transperineal or TRUS-guided aspiration +/- sclerosant
- open
- laparoscopic or robotic } not for infected abscesses

What are the potential complications of TUR of SV cysts or abscesses?

- reflux
- PV dribbling
- UTI
- bleeding

Chapter #35 – Renal Physiology and Pathophysiology

RENAL PHYSIOLOGY

Renal Blood Flow and GFR

Describe the arterial blood supply of the kidney (no collaterals → end arteries**)**

- renal artery
- gives off branches → adrenal, renal pelvis, ureter
- segmental → most commonly;
 - 1 posterior (branches before entering hilum, so posterior to renal pelvis)
*** can cause UPJO if crosses anterior to ureter ***
 - 4 anterior (apical, upper, middle, lower → variability)
- lobar
- interlobar (run through columns of Bertin)
- arcuate (run along corticomedullary jxn)
- interlobular
- afferent arteriole (to glomerulus) → efferent to vasa recta

Describe the venous drainage of the kidney (+collaterals **)**

- efferent arteriole → vasa recta
- interlobular (communicate freely via subcapsular plexus)
- arcuate
- interlobar
- lobar
- segmental (parallels segmental arteries; due to collaterals, can be sacrificed)
- renal vein

What is RBF?

- renal blood flow } **20% of cardiac output**
- regulated by changes in vascular resistance of all arteries up to & including efferent arteriole
- not evenly distributed } flow to outer cortex is 2-3x greater than inner cortex, which is
2-4x greater than medulla (medulla most vulnerable to ischemia)

What is RPF?

- renal plasma flow
- less than RBF } **$RPF = RBF \times [1-Hct]$**
- varies with hematocrit } higher Hct = lower RPF

What is GFR?

- **reflection of overall renal function**
- determined by both **hydrostatic & oncotic pressure** (Starling's forces) differences between the glomerular capillary and Bowman's space
- also affected by permeability of glomerular membrane
- **N GFR in males is ~125 mL/min and N in females is 100mL/min**

What factors affect GFR?

- 1) **transglomerular pressure** } **most important factor**
 } dependant on systemic BP but moreso on intraglomerular
 capillary pressure (afferent & efferent arterioles)
- 2) RPF } increase in RPF leads to increase in GFR
- 3) glomerular permeability } reduction in permeability = reduction in GFR
 } increased permeability DOES NOT lead to increased GFR
 (glomerulus at max permeability to water/solutes already)
 → does lead to increased filtration of larger molecules not
 normally filtered eg albumin
- 4) oncotic pressure } least important factor
 } normally, plasma proteins are not filtered across the glomerular membrane so
 oncotic pressure within Bowman's space is ~0

How does the body regulate GFR?

→ GFR is maintained relatively constant despite large fluctuations in systemic BP & RBF

- 1) **autoregulation**
 - occurs likely related to stretch receptors (ATP-mediated) and AT II
 - rise in MAP causes constriction of **afferent arteriole**, and vice versa
 - **results in maintenance of intraglomerular capillary pressure**
 - MAP <70mmHg leads to decreased GFR
 - MAP <40mmHg leads to stoppage of filtration
- 2) **tubuloglomerular feedback**
 - macula densa (DCT) senses ultrafiltrate levels (Na and Cl)
 - increased delivery of Na & Cl to distal tubule results in constriction of afferent arteriole and subsequent decrease in RPF
 - mediated by AT II via adenosine, TXA, NO effects on afferent arteriole

*** under abN conditions, however, neurohumoral responses become more important (NE & AT2) ***

How do you measure GFR?

- can't be measured directly }
 - 1) renal clearance eg CrCl
 - 2) plasma markers eg creatinine, cystatin C
 - 3) formulae eg Cockcroft-Gault, MDRD

What are the renal clearance markers used to measure GFR?

- 1) inulin (best but not feasible)
- 2) creatinine
- 3) radiolabeled compounds (eg DTPA)

What are the characteristics of the ideal substance to estimate GFR?

- 1) stable plasma concentration
- 2) freely filtered across glomerulus
- 3) not secreted, reabsorbed, synthesized, or metabolized by tubules
- 4) not removed from plasma by another method

Why is urinary creatinine less accurate than inulin to estimate GFR?

- some creatinine is secreted through PCT
→ **so creatinine overestimates GFR by 10-20%**
- therefore CrCl should be considered the upper limit of true GFR
→ **normal CrCl is ~120-140 mL/min**

Which plasma markers are used as surrogate markers of GFR?

- 1) creatinine } production rate depends on muscle mass and so there is no single “normal” creatinine that reflects “normal” GFR
→ must be individualized for each patient
} generally, 50% reduction in GFR = doubling of creatinine
- 2) plasma urea } highly variable and influenced by dehydration, high-protein diets, and increased tissue breakdown
} not as reliable as plasma creatinine
- 3) plasma cystatin C } constant production rate not affected by diet & clearance not affected by tubular functions
} **not widely available but BETTER THAN CREATININE**

What are some limitations of using plasma creatinine to estimate GFR?

- as GFR falls, tubular secretion increases to get rid of elevated creatinine, so plasma creatinine may not rise that much until GFR drops off significantly
- creatinine production increases in states of increased muscle breakdown (eg rhabdomyolysis) or with increased dietary protein so plasma creatinine may underestimate true GFR
- creatinine production may decrease with liver cirrhosis, leading to overestimation of true GFR

What formulae are used to improve the accuracy of plasma creatinine estimation of GFR?

→ to be accurate, total creatinine should be 1mg/kg/hr

- 1) Cockcroft-Gault
$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{IBW in kg})}{\text{Pcr (mg/dL)} \times 72} \times 0.85 \text{ (women)}$$

→ serum creatinine, age, sex, weight
- 2) modification of diet in renal disease (MDRD)
$$\text{GFR} = 186 \times (\text{Pcr}) \times (\text{age}) \times (0.742 \text{ if female}) \times (1.21 \text{ if Black})$$

→ serum creatinine, age, sex, race
- 3)
$$\text{GFR} = \frac{\text{Urine Cr} \times \text{urine volume}}{\text{serum creatinine}}$$

What are the 8 main functions of the kidney? }} “WEB DECAF”

- 1) **W**aste excretion
- 2) **E**lectrolyte regulation
- 3) **B**P control
- 4) **D**rug metabolism
- 5) **E**po production
- 6) **C**a and **P**O₄ metabolism (1,25-dihydroxyVit D)
- 7) **A**cid-base regulation
- 8) **F**luid homeostasis

Hormonal

Which hormonal substances cause VASOCONSTRICTION of the renal vasculature? } } } "A VANE"

- 1) **AT II** } acts mainly on efferent arteriole
 } **causes efferent vasoconstriction, aldosterone release, and Na retention**
 } may also cause intrarenal vasodilation to protect against renal ischemia
- 2) **Vasopressin** } potentiates vasoconstrictive effects of NE
 } **preserves renal function at low doses used for septic shock** but can induce renal ischemia at high doses
 } acts via vasopressin V1 receptor
- 3) **ANP** } produced by atria in response to volume expansion
 } **↑'s GFR (by efferent arteriolar vasoconstriction & afferent vasodilation) and ↑'s natriuresis (by ↑'d GFR, ↓'d renin & ↓'d aldosterone)**
 } preserves GFR during bilateral obstruction by dilating vessels that have been precontracted by NE, AT II or vasopressin
 } ↓'s endothelin and SVR
- 4) **NE** } causes vasoconstriction in all renal vessels
 } **preserves and may improve renal fxn when used during systemic vasodilation**
 } mediated via α_1 receptor
- 5) **Endothelin** } **most potent vasoconstrictor**
 } 3 isoforms and ET-1 is best described
 } ET-1 release is stimulated by ATII, ADH, thrombin, cytokines, reactive O₂ species, and shearing forces on vascular endothelium
 } ET-1 **stimulates aldosterone, +ve inotrope & chronotrope, releases ANP, and decreases RBF and GFR**
 } **despite reduction in RBF, Na excretion is increased**

Which hormonal substances cause VASODILATION of the renal vasculature? } } } "NO CO GAPS"

- 1) **NO** } made from reaction b/w arginine, NADPH, and O₂ to produce citrulline, NADP, water, and NO (reaction catalyzed by NOS)
 } **eNOS (or NOS-3) found in vascular endothelium and the NO made there causes vasodilation and vascular remodeling (via cGMP)**
 } increased eNOS activity can mitigate cyclosporine-related chronic allograft nephropathy and protect the kidney from reperfusion injury
 } increased iNOS is bad and can cause glomerular damage
- 2) **carbon monoxide** } heme oxygenase catalyzes the heme degradation reaction that results in the formation of Fe, CO, and biliverdin
 } **produces vasodilation in the kidney and can counteract the catecholamine-induced vasoconstriction**
 } high expression in medulla & helps maintain renal medullary flow
 } **also is renoprotective from oxidant injury (eg reperfusion injury)**
- 3) **Glucocorticoids**
- 4) **Acetylcholine**
- 5) **PG E₂**
- 6) **Serotonin/bradykinin**

Describe the RAAS?

- angiotensinogen (from liver) is converted by renin (from JGA cells in afferent arteriole) to AT₁
 → JG apparatus includes afferent arteriole + DCT
- AT₁ is converted by ACE (lungs, kidneys, small bowel, uterus) to AT₂
- AT₂ stimulates aldosterone release (from adrenal cortex – z. glomerulosa)

How do ACE inhibitors affect RBF & GFR?

- increased RBF
- decreased GFR in pathologic states (eg RAS)

What are the effects of AT II?

- 1) kidney → **EFFERENT arteriolar vasoconstriction** } to maintain GFR
 - ↓'s **renin secretion** (negative feedback)
 - **tubular water & Na reabsorption** } at high []'s, inhibits Na reabsorption in PCT
 - mesangial cell contraction to decrease glomerular filtration coefficient
 - ↓'s **medullary blood flow** resulting in concentration of urine
 - plays a role in **fetal renal development**
- 2) vascular → **peripheral vasoconstriction** (kidney, skin, mesentery, coronaries, brain)
- 3) adrenal → stimulates **aldosterone secretion** } Na reabsorption
- 4) CNS → increased BP, **thirst, and salt appetite**
 - increased secretion of corticotropin, prolactin, oxytocin, vasopressin

What are the 3 isoforms of NOS?

- neuronal NOS (nNOS or NOS1) } Ca dependent
- inducible NOS (iNOS or NOS2) } **Ca INDEPENDENT**
- endothelial NOS (eNOS or NOS3) } Ca dependent

How does the kidney control erythropoiesis?

- basal RBC production is ~10RBCs/hr } formation of mature RBCs takes ~2weeks
 - erythroid progenitor cells, proerythroblasts, retics, mature RBCs
- EPO is mainly **produced in the kidney (90%) but also in the liver (10%)**
- renal EPO is made by **interstitial fibroblasts and PCT cells** in response to anemia or hypoxia
- mediated by HIF-1 α

How does the kidney regulate Ca and PO₄ metabolism?

- **Vit D₃ (cholecalciferol)** comes from **diet** and from the **skin** (sun exposure)
 - inactive
- Vit D₃ is first hydroxylated in the **liver** to form **25-hydroxycholecalciferol (calcidiol)**
 - slightly active
- calcidiol is then filtered and reabsorbed by the **kidney** and then a 2nd hydroxylation occurs in the tubules to form the active **1,25-dihydroxycholecalciferol (calcitriol)**
 - PTH activates Vit D via 1 α -hydroxylase
 - 100x more active than calcidiol
 - can also be hydroxylated to inactive 24, 25-dihydroxycholecalciferol

What are the 4 main functions of active Vit D (calcitriol)?

- 1) gut } increased Ca absorption (small increase in PO₄ absorption)
- 2) bones } regulates osteoblast activity
- 3) kidney } increased reabsorption of Ca
- 4) parathyroid gland } suppresses PTH release

What factors control Vit D production?

- stimulates
 - hypoCa
 - PTH
 - hyperPO₄
- inhibits
 - hyperCa

What are the 2 main functions of PTH?

- 1) bone } when present continuously, it causes bone resorption, increasing serum Ca and PO₄
 - 2) kidney } ↑'d Ca reabsorption in DCT \
 - } ↓'d PO₄ reabsorption in PCT } PTH acts on **1α-hydroxylase** enzyme found
 - } stimulates calcitriol production / in the kidney
- **Ca reabsorption in Thick AL is NOT PTH-dependent**

What factors control PTH release?

- stimulates
 - hypoCa
 - hyperPO₄
- inhibits
 - hyperCa
 - calcitriol (Vit D)

What are the effects of ADH on the kidney?

- ADH is made by posterior pituitary gland ("POV")
- **increases passive reabsorption of water in the CCD via aquaporin-2 water channels**
- if inappropriately high ADH levels, HYPONATREMIA can result

What are the affects of ADH?

- water reabsorption in CCD
- ↑'d systemic vascular resistance
- Na reabsorption
- K excretion
- urea reabsorption
- ↑'d PG synthesis
- ↑'d ACTH secretion
- release of factor 8 and vWF from vascular endothelium

What factors control ADH release (CHART)?

→ **2 main stimuli are hyperosmolality (Na) and decreased ECFV**

- stimulates
 - hypovolemia
 - hyperosmolality
 - stress (eg pain)
 - nausea
 - pregnancy
 - hypoglycemia
 - drugs (nicotine, morphine, vincristine, diuretics, cisplatin, etc)
- inhibits
 - hypo-osmolality
 - hypervolemia
 - EtOH
 - phenytoin
- if you have both decreased ECFV and hypoNa, pressure receptors override osmoreceptors and decreased ECFV results in ADH stimulation
eg CHF (ADH secretion despite hypoNa)

Renal Tubular Function

What are the 2 basic functions of the renal tubule?

- 1) **reabsorption** \ can occur either via transcellular (eg Na and water) or
 - 2) **secretion** / paracellular (eg K, Ca) pathways
- **most reabsorption of HCO_3 and ions occurs in PCT**

What occurs in each part of the renal tubule?

- 1) PCT } **reabsorption of 60% of glomerular filtrate**
 - 65% of Na, K, Ca } **only Na is actively reabsorbed (Na-K-ATPase pump)** while all others are passively reabsorbed via Na-coupled transport
 - } **Ca reabsorption is mostly passive & Na-dependent**
 - 80% of PO_4 , **water & HCO_3** } gradient created by Na reabsorption facilitates **passive H_2O reabsorption**
 - } **~90% of filtered HCO_3 & PO_4 are reabsorbed in PCT**
 - **100% of glucose & amino acids** } **glucosuria if serum glucose >200mg/mL**
 - } secretion of **drugs and toxins** too large to be filtered
 - } generation of **ammonium** necessary for urinary acidification
 - 2) loop of Henle } **loop as a whole reabsorbs 25-30% of filtered Na and reabsorbs NaCl more than water to establish concentrated medullary interstitium needed for the excretion of a concentrated final urine**
 - } 4 main segments
 - thin descending limb } water (aquaporin-1 channels)
 - thin ascending limb } NaCl and urea
 - medullary + cortical ThickAL } more active reabsorption than thin limbs
 - } Na (20-25%), Cl, Ca (15%), **Mg (60-70%)**, K, HCO_3 (10-20%)
 - } **Ca reabsorption in thick AL is Na-dependent & INDEPENDENT of PTH**
 - } Thick AL also the site of **Tamm-Horsfall mucoprotein (uromodulin) secretion**
 - } **loop diuretics** act on **Na/K/Cl transporter (ThickAL)** → diuresis + NaCl loss
 - 3) distal tubule } **primarily involved in Na (5-10%) and Ca (10-15%) reabsorption**
 - } 2 segments → DCT and connecting tubule
 - } **thiazide diuretics** work here by inhibiting **Na/Cl cotransporter**
 - } Na reabsorption in DCT regulated by luminal Na [] not hormonal influences
 - } Na reabsorption in connecting tubule is regulated by **aldosterone** (like CCD)
 - } **Ca reabsorption in DCT is mainly PTH-REGULATED and NOT Na-dependent**
 - 4) collecting tubule } responsible for final changes in urine composition (related to diet)
 - } **ADH** upregulates AQP-2 water channels in the collecting tubule and increases water reabsorption
 - } **2 segments → CCD and medullary collecting tubule (MCT)**
 - } CCD consists of **65% principle cells (NaCl reabsorption) + 35% intercalated cells (acid-base secretion)**
 - Na reabsorption in CCD is regulated by **aldosterone** via upregulation of ENaC channels
 - **amiloride** blocks ENaC channels } K-sparing
 - **spironolactone** inhibits aldosterone } K-sparing
 - type A (H^+ secretion) & type B (HCO_3 secretion) intercalated cells
 - carbonic anhydrase uses $\text{H}_2\text{O} + \text{CO}_2$ to produce H^+ & HCO_3
 - } MCT has outer and inner segments
 - **ADH** causes increased urea reabsorption in inner MCT, which allows for high [] of urea in interstitium (osmotic gradient)
- *** acid-base balance is mainly regulated in CCD*****

What are the basic steps used to develop the countercurrent mechanism in the renal medulla?

- kidney is responsible for preservation of body H₂O by being able to [] urine (max 1200 mOsm/kg)
- to generate concentrated urine, kidney must be able to generate interstitial osmotic gradient of similar degree

- 1) medullary interstitium is made hyperosmolar by **reabsorption of NaCl (w/o water) in ascending loop of Henle**
- 2) countercurrent configuration (hairpin) of the loop allows for increased concentrating ability
- 3) in the presence of ADH, urea diffuses from collecting tubule to interstitium, increasing interstitial osmolarity even further (more water reabsorption in descending loop and more NaCl reabsorption in ascending loop)
- 4) medullary collecting tubule and loop are impermeable to water so this doesn't decrease the interstitial osmolarity. Water is reabsorbed mainly in cortex. Vasa recta are also arranged in hairpin loop that allows for water removal without removal of interstitial solutes

Where does the majority of reabsorption of the different electrolytes occur?

- 1) Na = 65% in PCT via Na-K-ATPase
- 2) K = 65% in PCT via Na-K-ATPase
- 3) Ca = 65% in PCT
- 4) HCO₃ = 90% in PCT
- 5) PO₄ = 90% in PCT
- 6) urea = 50% in PCT
- 7) glucose = ~100% in PCT
- 8) Mg = **65% in thick ascending limb of loop**

Which diuretics are K-wasting and which are K-sparing?

- wasting } loop diuretics (eg lasix, torsemide)
- } thiazides (eg HCTZ, metolazone)
- } carbonic anhydrase inhibitors (eg acetazolamide)
- sparing } spironolactone
- } amiloride
- } triamterene

How do loop & thiazide diuretics work?

- loop diuretics
 - **inhibits Na/K/Cl cotransporter in loop**
 - increased diuresis
 - increases excretion of Na, K, Cl, Ca, Mg
 - impairs concentrating ability
- thiazide diuretics
 - **inhibits NaCl cotransporter in DCT**
 - reduces GFR and RBF
 - stimulates Ca reabsorption by DCT
 - anti-diuretic effect in DI

What is the significance of Tamm-Horsfall mucoprotein (aka uromodulin)?

- secreted in **TAL of loop of Henle**
- forms matrix of all urinary casts and helps prevent UTIs
- decreases COM stones
- implicated in cast nephropathy, medullary cystic renal disease, & familial juvenile hyperuricemic nephropathy

Where is Ca reabsorbed in the kidney?

- | | | | |
|-----------------------|--------------------------|---|---|
| - 65% in PCT } | passive PTH-regulated | \ | Ca not reabsorbed in thin ascending or descending limbs of loop of Henle |
| - 15% in Thick AL } | NOT PTH-dependent | | |
| - 10-15% in DCT } | active PTH-regulated | | |
| - minimal in CD } | active PTH-regulated | | |

What is Bartter's syndrome?

- **AR disorder** characterized by:
 - 1) volume depletion
 - 2) low BP
 - 3) hyper-reninemic hyperaldosteronism
 - 4) metabolic alkalosis
- due to mutation in Na-K-2Cl and ROMK channels
- also see hypercalciuria (decreased Ca reabsorption in TAL)

What is Gitelman's syndrome?

- variant of Bartter's syndrome
- characterized by:
 - 1) volume depletion
 - 2) hyperCa (from increased resorption)
- mutation in Na-Cl cotransporter

What is Liddle's syndrome?

- AD syndrome characterized by:
 - 1) HTN
 - 2) hypoK (renal wasting)
 - 3) low renin
 - 4) low aldosterone
- due to mutation in Na channel in CCD leading to abnormal Na absorption and K secretion
- Rx is amiloride (blocks Na channel)

RENAL PATHOPHYSIOLOGY

Na and Water Imbalances

What is hypoNa? } **most common electrolyte abN'ity**

- **EXCESS WATER not handled by N compensatory mechanism (thirst & ADH suppression)**
- **serum Na <135 mEq/L**
- usually asymptomatic unless severe (<120 mEq/L)
 - can cause lethargy, N/V, seizures, altered mental state, coma, and death
- **spurious hypoNa can be seen with hyperlipidemia or hyperglycemia**

What are the causes of hypoNa?

- 1) ECFV depletion (hypovolemic - ↓'d water and ↓↓'d Na)
 - a) renal losses
 - urinary Na is >20 mmol/L (kidney can't keep Na)
 - excess diuretics
 - salt-wasting nephropathy
 - metabolic alkalosis
 - aldosterone deficiency
 - RTA type 2
 - osmotic diuresis (glucose, urea, mannitol)
 - b) extra-renal losses
 - **urine Na is <10 mmol/L (kidney tries to keep Na)**
 - vomiting
 - diarrhea
 - 3rd spacing from burns/trauma
 - pancreatitis

Rx → isotonic saline
- 2) mild ECFV excess (no edema; euvolemic - ↑'d water and ~normal Na)
 - urine Na is >20 mmol/L (kidney doesn't sense anything)
 - cortisol deficiency
 - hypoT4
 - **SIADH**
 - pain psychosis
 - drugs

Rx → water restriction
- 3) ECFV excess (edema; hypervolemic - ↑↑'d water and ↑'d Na)
 - a) renal (ARF & CRF)
 - urine Na is >20 mmol/L (kidney can't keep Na)
 - b) non-renal
 - **urine Na is <10 mmol/L (kidney tries to keep Na)**
 - nephrotic syndrome
 - CHF
 - cirrhosis
 - TUR syndrome

Rx → water restriction

What is the management of hypoNa?

*** **Na deficit = body wt (kg) x [125 – plasma Na] x 0.5 (0.6 in women)** ***

- 1) treat underlying cause
- 2) correct water imbalance
 - acute } water restriction + hypertonic saline (3%) at 1-2 mL/kg/hr + lasix
 - } frequent serum lytes & urine lytes
 - } raise serum Na by max 25 mEq/L over 48hrs at max rate ≤2 mEq/L/hr
 - chronic but severe/symptomatic } water restriction + hypertonic saline (3%)
 - } frequent serum lytes & urine lytes
 - } max correction rate <8-12 mEq/L/day
 - } stop aggressive Rx once Na ↑'d by 10% or symptoms subside
 - chronic & asymptomatic } rarely <48hrs
 - } no immediate correction needed
 - } water restriction
 - } demeclocycline (300-600 mg bid) or urea (15-60g od)
- 3) watch for **central pontine demyelination syndrome** seen w/ rapid correction of chronic hypoNa

What are the causes of SIADH (CHART)?

1) CNS

- brain tumours
- head trauma/SAH
- meningitis/encephalitis
- MS
- SDH
- hydrocephalus
- Shy-Drager syndrome
- GBS
- Rocky mountain spotted fever
- delirium tremens
- hypothalamic sarcoidosis
- olfactory neuroblastoma

2) Pulmonary

- pneumonia
- asthma
- pneumothorax
- lung abscess
- CF
- TB
- aspergillosis

3) tumours

- lung
- brain
- prostate
- thymoma
- TCC (ureter, bladder)
- duodenum
- lymphoma
- pancreas

Rx → demeclocycline, Lithium (irreversible)

What are the main features of SIADH?

→ **diagnosis can't be made if on diuretics OR if abN renal, adrenal, or thyroid function**

- hypoNa (≤ 125)
- low serum osmolality (< 280 mOsm/kg)
- concentrated urine (≥ 100 osm/L)
- UNa ≥ 20 mmol/L
- N renal function

What is hyperNa?

- **inability to concentrate urine + inadequate water intake } LACK OF WATER**
→ nonspecific symptoms that overlap with hypoNa
- most patients with intact thirst mechanism and free access to water can prevent hyperNa

What are the causes of hyperNa?

1) low total body Na (hypovolemic - ↓↓'d water and ↓'d Na)

a) renal losses

- urine Na > 20 mEq/L
- diuretics
- post-obstruction
- intrinsic renal disease

b) extra-renal losses

- **urine Na < 10 mEq/L**
- dermal (sweating, burns)
- GI (diarrhea, fistulas)
- Rx → hypotonic saline

2) normal total body Na (euvolemic - ↓'d water and ~normal Na)

a) renal losses

- **urine Na variable**
- **nephrogenic DI** - hypodipsia and partial DI
- **central DI**

b) extra-renal losses } respiratory and dermal insensible losses

- **urine Na variable**

Rx → water replacement

3) increased total body Na (hypervolemic - ↑'d Na)

- urine Na > 20 mEq/L

a) primary hyperaldosteronism (eg Conn's)

b) Cushing's syndrome

c) excessive exogenous Na } hypertonic dialysis, hypertonic NaHCO₃, NaCl tablets

Rx → diuretics + water replacement

What is the management of hyperNa?

→ **correct fluid deficit, replace water, and reverse underlying cause**

*** **Water deficit = body wt (kg) x [(plasma [Na]/140) - 1] x 0.5 (0.6 in women)** ***

- 1) treat underlying cause (eg desmopressin intranasal for central DI)
- 2) correct water imbalance
 - 1/2 NS if hypovolemic
 - asymptomatic } oral hydration with water if able
 } iv fluids + Na restriction
 - symptomatic } modest Na restriction
 } thiazide diuretics
 } NSAIDs
 } max rate of Na decrease is 2 mOsm/L/hr
- 3) watch for **cerebral edema**

What is Diabetes Insipidus?

- rare disease involving ADH that leads to high output of diluted urine & polydipsia
- 2 types are
 - central DI (more common) } posterior pituitary can't make ADH
 - nephrogenic DI } kidneys can't respond to ADH

List causes of nephrogenic DI. }}} "OLD CARP FISH"

- | | | |
|------------------|----------------------------|-----------------------------------|
| - Obstruction | - Calcium excess (hyperCa) | - Familial X-linked disorder (XR) |
| - Lithium | - Ampho B/Amyloid | - Idiopathic |
| - Demeclocycline | - Renal failure | - Sickle cell disease |
| | - PCKD | - HypoK |

What are the main features of Nephrogenic DI?

- hyperNa
- high serum osmolality (>280 mOsm/kg)
- dilute urine (<200 mOsm/kg)
- UNa ≥20 mmol/L
- High/normal ADH levels

List GU manifestations of sickle cell disease/trait.

→ **HUGE F'N PRIAPISM**

- Hematuria (dysmorphic RBCs) } M > F and L side 4x more than R
- UTIs
- Glomerular disease (MPGN, immune complex GN, etc) } leads to proteinuria
- ED
- Frequency, polyuria, etc (Nephrogenic DI)
- Nocturnal enuresis
- Priapism
- RTA (distal)
- Infertility
- ARF
- Papillary necrosis
- Infarcts (renal medulla, testicular)
- Slow (chronic) renal failure
- Medullary RCC (trait)

What are the causes of hypoK?

1) GI losses

- $$\left. \begin{array}{l} \text{---} \\ \text{---} \end{array} \right\}$$

What is the management of hypoK?

- spurious hyperK can be due to lab error, hemolysis, leukocytosis, thrombocytosis

1) increased input

- ## What is the management of hyperK?

- 1) treat underlying cause + stop all exogenous K

- 2) K-binding resins and K excretion } Kayexalate or Resonium
 } lasix
- 3) shift K into cells } 20u insulin + 1amp D5O (monitor blood sugar afterwards)
 } β-agonist → nebulized albuterol (Ventolin)
 } Na HCO₃ if acidotic patient
- 4) cardioprotection } 1 amp Ca gluconate
- 5) hemodialysis if refractory

Acid-Base Metabolism

What is the normal blood pH?

- **7.35 to 7.46** } maintained by kidney and lungs

What are the main sources of acid in the body?

- metabolism of carbs and fats (CO₂)
- metabolism of protein

What are the 3 main mechanisms the body can use to handle an acid load?

- 1) CO₂ excretion by lungs
- 2) buffers in the blood (HCO₃ and HgB) } most immediate response
- 3) H⁺ excretion by kidneys
 - Na⁺/H⁺ pump and H⁺/ATPase proton pump are responsible for **reabsorption of HCO₃ (80% in PCT) and secretion of H⁺ into urine (DCT + collecting duct)**
 - ammonium (NH₄⁺) excretion also helps secretion of H⁺

What are the 3 main mechanisms the body can use to handle an alkali load?

- 1) respiratory compensation (hypoventilation)
- 2) buffers in blood
- 3) renal excretion
 - **increased concentration of HCO₃ in glomerular filtrate**
 - weakening of acidification of PCT due to alkalemia

What is the Henderson-Hasselbach equation?

- defines the HCO₃ buffer
- $\text{pH} = 6.1 + \log [\text{HCO}_3] / 0.03\text{PCO}_2$
- non-logarithmic terms **$[\text{H}^+] = 24 \times \text{PCO}_2 / [\text{HCO}_3]$**

What are the 5 main factors that regulate H⁺ secretion in the kidney?

- 1) hypovolemia } leads to Na retention and increased HCO₃ absorption
- 2) low K and low Cl } increases HCO₃ reabsorption
- 3) elevated pCO₂ } leads to increased renal H⁺ secretion
- 4) high aldosterone } indirectly increases H⁺ excretion by increasing Na⁺ absorption
- 5) reduced GFR } less filtered HCO₃ leads to increased H⁺ excretion

What are the 4 main factors that regulate HCO₃ reabsorption in the kidney?

- 1) arterial pCO₂
- 2) luminal HCO₃ concentration
- 3) luminal flow rate
- 4) AT₂

Acid-Base Disorders

What is metabolic acidosis?

- loss of HCO_3 leads to systemic acidemia } **low pH and low HCO_3**
- appropriate compensation is hyperventilation } **reduction of pCO_2**
- can be anion gap metabolic acidosis or NAG metabolic acidosis
 → anion gap = $\text{Na} - (\text{Cl} + \text{HCO}_3)$ } normal is ≤ 12

What are the causes of metabolic acidosis?

- 1) AG } DKA
 } lactic acidosis
 } ingestions } methanol, salicylate, formaldehyde, ethylene, glycol, paraldehyde, toluene, sulfur
 } massive rhabdomyolysis
- 2) Non-AG } GI losses (diarrhea, pancreatitis, ureterosigmoidostomy, cholestyramine)
 } renal losses (RTA)
 } acid loading (TPN, ammonium chloride)

What is RTA?

- **family of syndromes due to defects in renal tubular H^+ secretion & urinary acidification**
- RTA type 1 } aka “classic RTA” or “distal RTA” (most common form)
 } **adults (2/3)** present with stones, whereas kids (1/3) present with FTT, vomiting, diarrhea
 } **defective H^+ ATPase in collecting duct (intercalated cells)**
 → failure of H^+ secretion in distal nephron even after NH_4 chloride load test
 } acquired (“POST CLAAASHH”) VS idiopathic VS congenital (uncommon - AD & AR)
 } **hyperCl + hypoK + NAG met. acidosis + high urine pH (>5.5) despite low serum HCO_3**
 } **hypocitraturia + hypercalciuria + hyperphosphaturia**
 → 70% get **Ca PO_4 STONES** (brushite) & **medullary nephrocalcinosis**
 } acidosis leads to **secondary hyperPTHism** from **hypoCa**
 → get metabolic bone disease
 Rx → K citrate or NaHCO_3
- RTA type 2 } aka “proximal RTA”
 } more common in **kids** (can get osteomalacia & growth retardation)
 } **defective HCO_3 reabsorption in PCT**
 → loss of HCO_3 in urine + overwhelming of distal H^+ secretion
 } sporadic (more common) VS congenital (less common)
 } **acidemia usually less severe** than type 1
 - DCT can still secrete H^+ to try to offset HCO_3 loss
 } **hyperCl + hypoK + NAG met. acidosis + N/low urine pH (slightly <5.5)**
 + **mildly low serum HCO_3 (15-20mEq/L)**
 } **N urine citrate levels (NO stones)**
 } often part of Fanconi’s syndrome
 → leak of phosphate, glycogen, amino acids, uric acid, protein
 } can also develop growth retardation & metabolic bone disease (more common than dRTA)
 Rx → NaHCO_3 + K supplementation
- RTA type 3 } considered variant of type 1 (distal + proximal issue)
- RTA type 4 } **impaired secretion of H^+ and K^+ in DCT**
 } associated with **HTN & CRF (DM, interstitial renal disease)**
 → often also associated with aldosterone deficiency or resistance
 } **hyperCL + hyperK + NAG met. acidosis + low urine pH (<5.5)**
 } NO stones (reduced renal excretion of stone-forming substances due to CRF)
 Rx → mainly directed at controlling hyperK
 → treat aldosterone deficiency (fludrocortisone)

List the causes of acquired distal RTA. } } } "POST CLAAASHH"

- Pyelo (chronic)
- Obstruction
- Sick cell anemia
- Transplant (renal)
- Cirrhosis
- Lithium
- Analgesic nephropathy
- ATN
- Autoimmune disease } thyroiditis, SLE, Sjogren's
- Sarcoidosis
- HyperPTH'ism
- Hypercalciuria (familial)

What is metabolic alkalosis?

- inability to get rid of systemic HCO_3^- } **high pH and high HCO_3^-**
- appropriate compensation is hypoventilation } **increased pCO_2**

What are the causes of metabolic alkalosis?

- 1) low urine Cl ($<15 \text{ mEq/L}$)
 - GI losses (NG suction, vomiting, laxative abuse)
- 2) high urine Cl ($>15 \text{ mEq/L}$)
 - renal losses (diuretics)
 - hyperaldosteronism
 - Cushing's syndrome
 - Bartter's syndrome (hypovolemic + low BP + hyper-renin hyperaldosteronism + metabolic alkalosis)

What is respiratory acidosis?

- due to inadequate respiration and overproduction of acid (CO_2) } **low pH and high pCO_2**
- appropriate compensation is renal reabsorption of HCO_3^- } **increased HCO_3^-**
 - acute } $1 \text{ HCO}_3^- : 10 \text{ pCO}_2$
 - chronic } $3.5 \text{ HCO}_3^- : 10 \text{ pCO}_2$

What are the causes of respiratory acidosis?

- 1) central depression of respiration
 - trauma
 - opiates
 - C-spine trauma
- 2) chest cavity problems
 - pneumothorax
 - pulmonary edema
- 3) upper airway obstruction

What are the clinical effects of elevated pCO_2 ?

- elevated ICP
- tachycardia
- central depression
- decreased LOC/coma

What is respiratory alkalosis?

- due to hyperventilation } **high pH and low pCO_2**
- appropriate compensation is renal loss of HCO_3^- } **decreased HCO_3^-**
 - acute } $2 \text{ HCO}_3^- : 10 \text{ pCO}_2$
 - chronic } $5 \text{ HCO}_3^- : 10 \text{ pCO}_2$

What are the causes of respiratory alkalosis?

- fever
- anxiety
- head trauma
- pain
- septicemia
- PE
- aggressive ventilation settings

Chapter #36 – Renovascular Hypertension and Ischemic Nephropathy

HISTORICAL BACKGROUND

What is the role of the RAAS?

- regulates BP
- regulates Na balance
- regulates K balance
- regulates GFR

DEFINITIONS

Hypertension

What is the WHO definition of HTN?

- sBP >160 or dBP >95 or both
- diagnosis requires multiple readings
- optimal to keep below 140/70

What are the causes of HTN? }}} “Essential AORTTA”

- 1) essential (85-90%)
- 2) Aortic coarctation (1%)
- 3) OCP (<1%)
- 4) Renal disease (5%) } parenchymal disease, renovascular disease
- 5) T₄ excess
- 6) Toxemia of pregnancy
- 3) Adrenal (5%) } Cushing's, Conn's, pheochromocytoma, etc

Renal Arterial Disease vs Renovascular HTN

What is the definition of RVH?

➔ **HTN resulting from a renal arterial lesion that is relieved by correction of the offending lesion or removal of the kidney**

- can have renal arterial disease w/o HTN and/or renal arterial disease that does not cause HTN
→ ie renal arterial disease ≠ RVH
- RVH is the 2nd most common correctable cause of 2° HTN (except for OCP)

PATHOLOGY AND NATURAL HISTORY

What are the 3 major pathological entities that cause renal arterial disease?

- 1) atherosclerosis (ASO) → 70%
- 2) fibrous dysplasia (FD) → 30%
 - intimal, medial, perimedial fibroplasias (all collagen related)
 - true fibromuscular hyperplasia (true hyperplasia of smooth muscle)
- 3) miscellaneous → renal artery aneurysms, AVM, middle aortic syndrome, etc

Table 36-1 -- Classification and Natural History of Renovascular Disease

Atherosclerosis: Proximal intimal plaques. Seen predominantly in males and usually in older age groups. Progressive in about 40% of patients; may dissect or thrombose. May involve renal arteries only or may involve carotid and coronary arteries, aorta, and other vessels.

Intimal fibroplasia: Collagenous disease involving intima; seen in children and young adults. Progressive; may dissect. May involve other vessels.

True fibromuscular hyperplasia: Diffusely involves media. Seen in children and young adults. Progressive. Radiographically indistinguishable from intimal fibroplasia. Very rare.

Medial fibroplasia: Series of collagenous rings involving media of main renal artery, often extending into branches. Usually seen in women in their 30s and 40s. Produces typical "string of beads" pattern in angiography. Does not dissect, thrombose, or rupture, and seldom progresses after 40 years of age. May involve other vessels.

Perimedial (subadventitial) fibroplasia: Dense collagenous collar involving media, just beneath adventitia of vessel. Tightly stenotic, with extensive collateral circulation on angiography. Seen mostly in women ("girlie disease"). Progressive. Involves renal arteries only.

Miscellaneous: Renal artery aneurysms, middle aortic syndrome, periarterial fibrosis, and post-traumatic intimal or medial disease. Variable in location and obstruction; occurs in diverse clinical settings.

Atherosclerosis

Describe atherosclerotic renal arterial disease?

- usually a **manifestation of systemic disease** rather than isolated renal artery atherosclerosis
- usually in **men and in older patients**
- usually **ostial or in the proximal 2cm of the renal artery** and is **bilateral**
- lesion **involves the intima** of the artery → eccentric plaque 66%
 - circumferential plaque 33%
- **can dissect or thrombose**
- **progressive in 40-50%** within 2years → rate of progression depends on initial degree of stenosis
 - progression common if >75% stenosis
 - BP can't be used as a marker of progression
- can lead to **complete renal artery occlusion in 10-15%**
- can eventually lead to ESRD → atherosclerosis-related ESRD patients respond poorly to RRT (worst survival group of all pt's on HD)

Intimal, Medial, and Perimedial Fibroplasia

What are the features of the different types of fibroplasia?

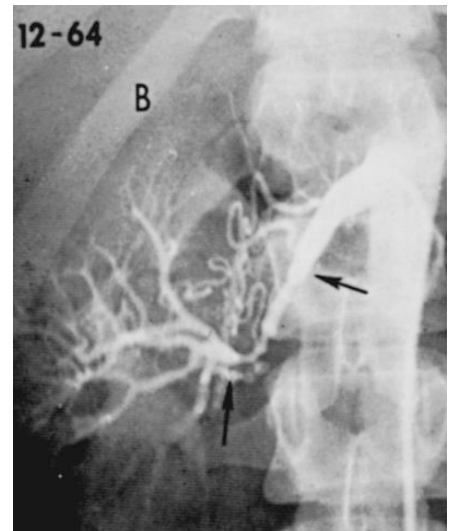
	Intimal	Medial	Perimedial (aka girly dz)
Age	Kids, young adults	older women (25-50yrs)	women 15-30yrs
Frequency	10%	80%	10%
Location	can be systemic	can be systemic	renal arteries only
Histology	circumferential accumulation of collagen	thinned & thickened media, muscle replaced by collagen	collar of dense collagen enveloping renal artery for variable lengths
associations	dissecting hematomas	Micro-aneurysms	uncommon
progression	progresses to occlusion	No progression to occlusion	progresses to occlusion
angiography	smooth, fairly focal, proximal or midportion stenosis	"string bead" appearance in distal 2/3 of main renal artery	may seem like beading but caliber of normal segment not exceeded by "beads"; extensive collaterals



→ INTIMAL FIBROPLASIA



→ MEDIAL FIBROPLASIA



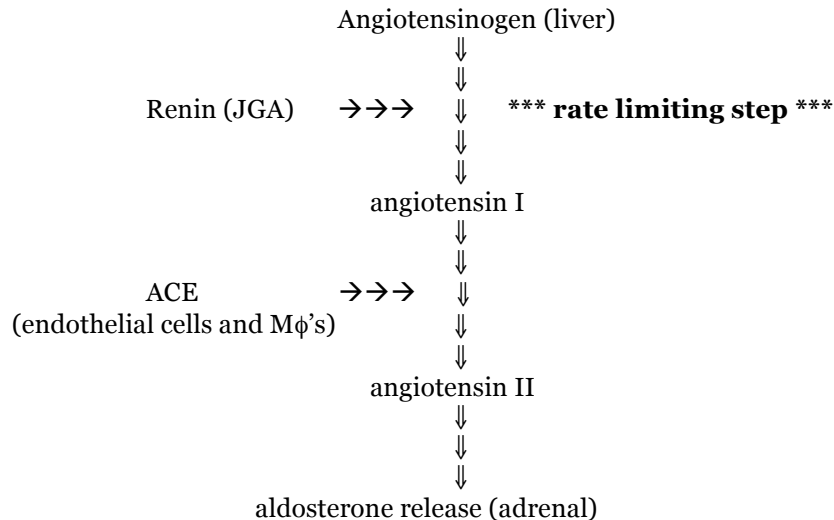
→ PERIMEDIAL FIBROPLASIA

What is fibromuscular hyperplasia?

- very rare disease } accounts for ~2% of fibrous renal artery disease
- **occurs in children and young adults**
- only renal arterial disease with **true hyperplasia** of smooth muscle } others have collagen
- concentric thickening of wall (media)
- **progresses to complete occlusion**
- smooth stenosis of renal artery or branches } **similar to intimal fibroplasia on imaging**

PHYSIOLOGY OF THE RAAS

Describe the Renin-Angiotensin-Aldosterone system.



What is angiotensinogen?

- 452aa serine protease inhibitor } primarily made in **liver**
- synthesis stimulated by estrogen, glucocorticoids, infection, or tissue injury

What is renin?

- single-polypeptide-chain aspartyl protease
- secreted by **juxtaglomerular cells of afferent arteriole in kidney (next to macula densa)**
- cleaves 1aa off angiotensinogen to form AT I

What are the factors that regulate renin secretion?

→ **renin secretion is the rate-limiting step and regulates activity of RAAS**

- 1) macula densa (osmoreceptor) → reduction of DCT salt delivery stimulates renin production
→ related to Cl concentration
- 2) baroreceptor → diminished JG cell stretch due to renal hypoperfusion stimulates renin production
- 3) neural → stimulation of β -adrenergic sympathetics in JG cells leads to renin secretion
- 4) endocrine/paracrine → PG E₂, I₂, and arachidonic acid stimulate renin secretion
→ **renin secretion inhibited by AT II, vasopressin, ANP, endothelin**
- 5) intracellular → increase in adenylate cyclase increases renin secretion
- via β -agonists, PG E₂, PG I₂, dopamine, histamine, PTH
- 6) disease states → steroids, thyroid, silicosis, sarcoidosis, etc

List 5 endogenous stimulators of renin release } } } "Salty BP BP"

- ↓'d **Salt** (NaCl) to macula densa (DCT)
- ↓'d **Blood volume** (JG cell stretch)
- ↓'d **Perfusion pressure**
- ↑'d **β 1**-adrenergic activity
- ↑'d **PGs**

What is angiotensin converting enzyme (ACE)?

- zinc-containing single chain glycoprotein enzyme
- cleaves 2 aa's off AT I and **forms AT II**
- **also inactivates bradykinins**
- found in various organs → high []'s in **lung, kidney, ileum, duodenum, uterus**
→ lung no longer considered only major site of action

Where does ACE act?

- kidney → glomerular endothelial cells and PCT brush border
- CNS → several locations
- adrenal → medulla
- reproductive tract → testes, prostate, ovary

What are the factors that regulate ACE activity?

- increased by } steroids, thyroid hormones, silicosis, primary biliary cirrhosis, sarcoidosis

What are the effects of AT II?

- 1) kidney → **EFFERENT arteriolar vasoconstriction } to maintain GFR**
→ ↓'s **renin secretion** (negative feedback)
→ **tubular water & Na reabsorption** } at high []'s, inhibits Na reabsorption in PCT
→ mesangial cell contraction to decrease glomerular filtration coefficient
→ ↓'s **medullary blood flow** resulting in concentration of urine
→ plays a role in **fetal renal development**
- 2) vascular → **peripheral vasoconstriction** (kidney, skin, mesentery, coronaries, brain)
- 3) adrenal → stimulates **aldosterone secretion** } Na reabsorption
- 4) CNS → **increased BP, thirst, and salt appetite**
→ increased secretion of corticotropin, prolactin, oxytocin, **ADH**
- 5) gonads → role not clear

What are the different AT II receptor subtypes?

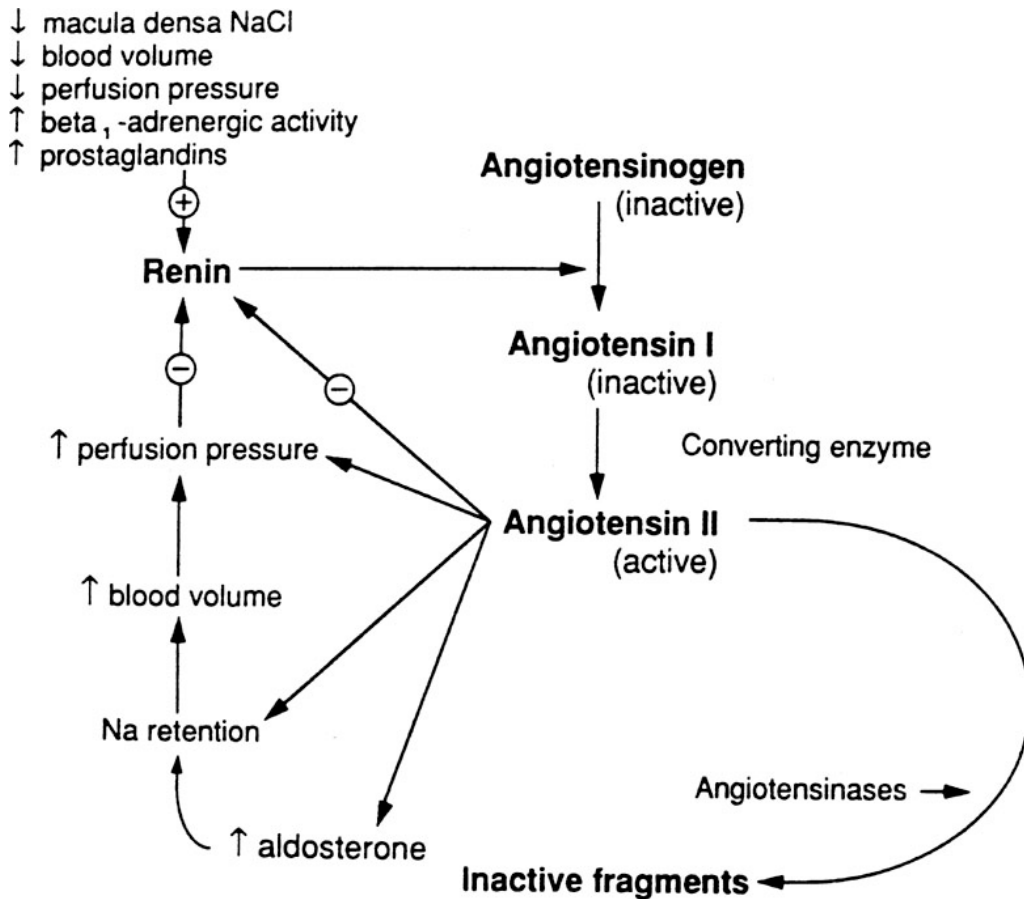
- 1) AT₁ → 360aa's, gene on chromosome 3
→ higher affinity for AT II than AT III
→ responsible for all the vascular effects of AT II (vasoconstriction, aldosterone release, B-adrenergic stimulation)
- 2) AT₂ → 360aa's, gene on chromosome X
→ equal affinity for AT II and AT III
→ may be antagonistic to AT₁ receptor
→ larger role in fetal life

What other angiotensins are there?

- AT 2 (angiotensin 1-8)
- AT 3 (angiotensin 2-8) → similar to AT II (lacks aspartyl aa at amine end)
- AT 4 → similar to AT I but lacks the 2 terminal amine ends
- angiotensin 1-7 → similar to AT I but lacks 3 aa's at carboxy end
→ acts in opposing fashion to AT II (ie vasodilation, natriuresis, etc)
→ formed from AT₁ by neprilysin } ACEi's increase angiotensin 1-7 levels

How do ACE inhibitors affect RBF & GFR?

- minimal affect on GFR unless there is RAS (then get decreased GFR)
- increased RBF



→ **KNOW THIS CHART**

PATHOPHYSIOLOGY OF RENOVASCULAR HTN

What are the Goldblatt experiments?

- classical experiments on RVH done in 1930's
- demonstrated HTN can be produced by constricting renal artery in dogs
- 2 kidney, 1 clip model → renal ischemia in clipped kidney results in RAAS activation
 - AT II mediated generalized vasoconstriction, systemic HTN, and 2° hyperaldosteronism (**acutely renin-dependent HTN**)
 - contralateral N kidney suppresses renin release and increases Na excretion (works against stenotic kidney)
 - euvolemia
 - ACE inhibitors decrease BP
 - once chronic phase is reached, contralateral kidney gets damaged too from high levels of AT II (**eventually results in volume-dependent HTN**)
- 1 kidney, 1 clip model → solitary ischemic kidney releases renin, activating RAAS
 - get systemic HTN and salt retention
 - hypervolemia
 - elevated BP, Na retention & hypervolemia gradually suppresses renin secretion
 - so get systemic HTN and Na retention despite normal AT II levels
 - ACE inhibitors don't help BP

What are the phases of renovascular HTN?

- 1) **acute → renin dependency**
- 2) **transitional** → progressive volume and Na retention
→ gradual onset of secondary hyperaldosteronism
→ thirst
→ progressive suppression of renin secretion
→ progressive decline of contralateral natriuresis
- 3) **chronic → volume expansion**
→ suppressed renin secretion
→ systemic vasoconstriction
→ increased sensitivity to AT II
→ increased vasopressin secretion
→ increased sympathetic activity
→ structural vessel wall changes
→ development of contralateral nephrosclerosis

HUMAN CORRELATES OF EXPERIMENTAL RENOVASCULAR HTN

What occurs in unilateral RAS?

- resembles to 2 kidney, 1 clip model
- activation of RAAS } results in systemic HTN + 2° hyperaldosteronism +/- hypoK
- relief of stenosis or Nx results in amelioration of HTN if carried out before “chronic phase” when contralateral kidney is damaged also

What occurs in bilateral RAS?

- mixed picture between the two models
- evidence of overactivity of RAAS (HTN responds to ACE inhibitors) as well as volume overload (diuresis after revascularization)
- likely due to asymmetrical development of RAS

Which disease processes resemble the 1 kidney, 1 clip model?

- RAS to solitary functioning kidney
- unilateral RAS with parenchymal damage to contralateral kidney (nephrosclerosis or atheroembolism)
- transplant RAS

PATHOPHYSIOLOGY OF ISCHEMIC NEPHROPATHY

What is ischemic nephropathy?

- **result of chronic hypoperfusion of total functioning renal mass**
 - **B/L severe stenosis or stenosis to a solitary kidney (anatomic or fxn'l)**
 - **can occur without HTN**
- pathophysiology is poorly understood → **not just a lack of oxygen and nutrients**
- renal perfusion below 70-80 mmHg results in loss of autoregulation
 - gradual deterioration of GFR } RAAS activation results in AT₂-mediated efferent arteriolar vasoconstriction
 - hemodynamically significant stenosis at **>70% stenosis**
- critical reduction of RBF results in IN without affecting renal viability because RBF is several fold higher than blood flow to other organs such as liver or heart
 - kidney develops collaterals from adrenal, lumbar, and ureteric vascular beds
- get a **decrease in size of kidney**
- may involve vascular mediators (endothelin, TXA, NO, prostacyclin), Ca accumulation or ATP depletion of ischemic cells, production of O₂ free radicals, etc

What are the structural changes seen in a chronically ischemic kidney?

- **tubular changes** → **most prominent finding**
→ **patchy tubular necrosis & atrophy**
- decrease in size of glomeruli with thickening of Bowman's capsule
- glomerular sclerosis
- hypercellularity of the JG apparatus
- arteriolar thickening and hyalinosis (as seen with essential HTN, DM, etc)

What is the significance of atheroemboli and ischemic nephropathy?

- renal cholesterol emboli usually occurs in older, HTN'sive patients with severe abdominal aortic atherosclerosis and contributes significantly to renal dysfunction in cases of IN
- **~70% spontaneous and 30% after inciting event** (aortic Sx, angiography, thrombolytic Rx)
- **50% of all cholesterol emboli result in renal manifestations** } 20-30% mortality rate
- atheromatous fragments lodged in vessels are very thrombogenic and leads to occlusion of vessels with inflammatory reaction + fibrosis
- variable severity → mild to rapid onset of ARF
- gradual improvement of renal fxn after emboli but recurrent emboli lead to progressive CRF

Which organs are most commonly affected by atheroembolism?

- kidney
- spleen
- pancreas
- GI tract

What are the cutaneous manifestations of cholesterol emboli?

- livedo reticularis (lacy blue discoloration affecting lower limbs)
- digital cyanosis or gangrene
- skin ulceration
- subcutaneous nodules
- retinal emboli (Hollenhorst's plaques)

What is the management of cholesterol emboli?

- supportive Rx } removal of inciting trauma if present
- } cessation of anticoagulation
- } control of HTN
- } start RRT as indicated
- prevention } avoid unnecessary/rough manipulation of atherosclerotic vessels
- } avoid prolonged anticoagulation in pts at risk

CLINICAL FEATURES OF RENOVASCULAR HTN

What are the features suggestive of true renovascular HTN? }} **A FARMERSS BP**

→ symptoms are rare, except flank pain related to segmental infarction or arterial dissection

→ renin-mediated

- Age } onset at age <30yrs or >55yrs (fibrous dysplasia or atherosclerosis)
- Family hx is negative } +ve FmHx suggests essential HTN
- Atherosclerosis (CAD, CVD, carotid disease, etc)
- Renal deterioration with ACE inhibitor
- Medication refractory, or suddenly worse
- Extreme HTN (accelerated, malignant HTN or HTN'sive crises)
- Retinopathy from HTN (grade 3 or 4)
- Smokers } higher incidence of smoking in RVH & FD than with essential HTN
- Sudden onset and shorter duration of HTN is suggestive of RVH } better chance of cure
- Bruit (upper abdominal)
- Pulmonary edema episodes

What lab tests are suggestive of RVH?

- 1) proteinuria } usually mild
→ can also be from DM, glomerulosclerosis, etc
- 2) hypoK } highly suggestive of RVH that results in 2° hyperaldosteronism
→ ~15% of RVH patients have hypoK
- 3) azotemia + atherosclerosis } suggestive of renal arterial cause of HTN

CLINICAL FEATURES OF ISCHEMIC NEPHROPATHY

Epidemiologic Considerations

What other conditions are associated with atherosclerotic RAS?

- generalized atherosclerosis obliterans (30-60%)
→ regardless of whether RVH is present
→ ~40% of these are significant (ie >50% stenosis)
- AAA (40%)
- aorto-occlusive disease (33%)
- lower extremity occlusive disease (40%)
- CAD (20%)
- DM2 (8%) } 2-fold higher → more likely to have bilateral disease too

Screening and Diagnosis

What are the 8 RFs predictive of atherosclerotic RAS?

→ A CCCP FAD

- 1) higher Age
- 2) CAD
- 3) CHF in the past
- 4) elevated Creatinine
- 5) PVD
- 6) Female
- 7) progressive Azotemia after BP control with meds
- 8) DM

*** HTN not helpful ***

Which patients should be screened for RAS?

- **older patients** with most or all of the following;
 - 1) evidence of generalized atherosclerosis
 - 2) decrease in size of one or both kidneys
 - 3) renal insufficiency with no obvious underlying cause
 - 4) progressive azotemia after restoration of normal BP with anti-HTN'sive meds
 - 5) CAD
 - 6) hx of CHF
 - 7) PVD
- **presence or absence of HTN should not influence decision to investigate**

Why does control of BP decrease renal function in pts w/ RAS?

- perfusion-dependent renal fxn } β -blockers cause a fall in CO
- } ACEi lead to loss of efferent arteriolar vasoconstriction tone

DIAGNOSTIC EVALUATION

What is the definitive test to diagnose RAS?

- angiography → gold standard

What are some other tests that are used to assess for RVH & IN?

- 1) **functional studies** that Dx hyperactivity of the RAAS but don't provide any anatomical info
 - plasma renin activity (PRA) } limited use
 - captopril test
 - captopril renography } best predictor of surgical cure & may localize ischemic kidney
 - RVR assays } can localize ischemic kidney
- 2) **anatomic studies** with no functional information
 - IVP } no longer used
 - Duplex U/S
 - MR angio
 - spiral CT angio
 - angiography } **gold standard**

What tests are used to assess for ischemic nephropathy?

- difficult to assess } lack of functional tests + inability to determine conclusively that an anatomic lesion in renal artery is cause of renal impairment
- } stabilization/improvement of renal fxn post-revascularization remains the final proof of IN → as long as ischemic damage is reversible

What is the role of intravenous urography in RVH?

- poor sensitivity & specificity so **NO LONGER USED**
- findings suggestive of RVH → **delayed appearance of contrast (most important)**
 - **renal size difference >1.5cm (most common)**
 - delayed hyperconcentration of contrast w/in collecting system
 - retention of contrast in non-obstructed system
 - notching of pelvicalyceal system by collateral vessels

What is the role of a peripheral PRA test in RVH?

- designed to diagnose RAAS overactivity } no anatomic info & not good for diagnosing IN
- need to stop anti-HTN'sives for 2 wks prior to test & also need to index PRA to sodium intake
- **limited use** } ~15% w/ essential HTN have elevated PRA & 20% w/ RVH have normal PRA

What is the role of a captopril test in RVH?

- designed to diagnose RAAS overactivity } no anatomic info
- measure peripheral PRA **before and after (1hr) oral captopril (25mg)**
- can take B-blockers, but need to stop diuretics and ACE inhibitors 1 week prior
- **+ve if** } **post-captopril PRA is >12ng/mL/hr** \ **not reliable in patients with**
 } **absolute increase in PRA >10ng/mL/hr** } **azotemia nor in kids**
 } **400% increase in baseline PRA** /
- limited use as screening tool } low sensitivity
- strength is high NPV } accurately excludes RVH

What is the role of captopril renography in RVH?

- designed to diagnose RAAS overactivity } can localize ischemic kidney
- need to stop ACE inhibitors 3-5 days before study
- loss of preferential vasoconstriction of efferent arteriole (mediated by AT II) in ischemic kidney results in loss of postglomerular pressure and thus, decreased GFR
- radionuclide renography measures this decreased GFR } **MAG3 is best radionuclide agent**
- oral captopril (25mg) and then renogram obtained 1hr after
- **+ve for RVH if:**
 - 1) **asymmetry of renal size and function**
 - 2) **captopril-induced changes** }
 - a) **delay in time to max activity (>11mins)**
 - b) **significant asymmetry of peak activity**
 - c) **marked cortical retention of radionuclide**
 - d) **marked decrease of ipsilateral renal GFR**
- **predictive of cure or improvement after revascularization**
- limited value if bilateral RAS, RAS to solitary kidney, or impaired renal function

What is the role of renal vein renins (RVR) in RVH?

- designed to diagnose RAAS overactivity } no anatomic info
- measures hypersecretion of renin from ischemic kidney and contralateral suppression of renin
 - blood samples taken from IVC and both renal veins in SUPINE position
 - **hypersecretion = PRA increase of >50%**
- if PRA high, but RVR fails to show >50% increment, then can sample from segmental renal veins to localize segment of kidney responsible
- can add captopril to accentuate renin secretion from ischemic kidney
- good for localizing ischemic kidney in unilateral RAS & the more ischemic kidney in B/L RAS

What is the role Duplex U/S in RVH?

- gives anatomic info only
- see turbulent jet during systole and decrease in diastolic flow
 - **peak systolic velocity (PSV) >180cm/sec** (normal is ~100cm/sec)
 - **renal-aortic ratio (RAR) of PSV >3.5 indicates severe stenosis (>60%)**
- advantages } noninvasive, no contrast req'd, no radiation, cheap, don't need to stop meds, not affected by azotemia
- disadvantages } dependence on operator skill, especially in obese patients

What is the role of MR angio in RVH?

- gives anatomic info only } some functional data (RBF, GFR)
- improved visualization of blood vessels with Gadolinium enhancement
- advantages } noninvasive, no radiation, no contrast
- disadvantages } image quality not as good as angio (especially distal arterial tree), expensive

What is the role of CT angio in RVH?

- advantages } cheap, convenient
- disadvantages } radiation, lots of contrast req'd, variable visualization of distal arterial tree

What is the role of contrast arteriography?

- **gold standard for Dx'ing RAS**
 - } advantages → can be diagnostic and therapeutic
 - } disadvantages → expensive, invasive, contrast use, radiation, requires arterial access
- decreased contrast load and catheter size with digital subtraction angio (DSA)
- CO2 and gadolinium also used to reduce contrast nephrotoxicity

What are the risks of arteriography?

- access → bleeding, hematoma, dissection, thrombosis, distal embolization of atherosclerotic plaque, cholesterol emboli
- contrast → allergic reaction, renal insufficiency, volume overload

COST-EFFECTIVE APPROACH FOR DIAGNOSIS

What is the recommended approach for RAS?

- 1) RVH → **high suspicion** → angio
→ if bilateral, can do RVR assays to localize ischemic side
→ **low or moderate** → captopril renography
→ if +ve, angio
→ if -ve but still suspicious, do duplex U/S, MRA, CTA
- 2) ischemic nephropathy → HTN may not be part of clinical picture
→ can't be diagnosed by functional testing
→ **pursue anatomic testing directly** } NO FXN'L TESTS for IN
 - strong suspicion → angiography
 - low or moderate → Duplex U/S, MRA, CTA
 - if +ve, do angio
 - if -ve but still suspicious, more testing

SELECTION OF PATIENTS FOR SURGICAL OR ENDOVASCULAR THERAPY

RVH

Which patients with FD-related RVH should be recommended surgical intervention?

- 1) **intimal or perimedial fibroplasia**
 - younger pts, progresses to occlusion, and hard to manage BP with meds
 - angioplasty if main renal artery
 - surgery if branch renal artery involved
- 2) **medial fibroplasia** } medical Rx is mainstay
 - doesn't progress to complete occlusion
 - **intervention only if BP hard to control with meds**

Which patients with atherosclerotic RVH should be recommended surgical intervention?

- 1) **BP hard to control on meds** } surgical Rx
- 2) **renal function threatened by advanced disease** } surgical Rx
- if older + extrarenal vascular disease } medical Rx

Ischemic Nephropathy

Which patients with IN should be recommended surgical intervention?

- 1) high grade (>80%) arterial stenosis **affecting ENTIRE renal mass** (B/L or solitary kidney)
- 2) unilateral atherosclerotic RAS + contralateral kidney with parenchymal disease
- 3) complete occlusion of renal artery + evidence that kidney is still viable

What are the 5 signs of renal salvageability in complete occlusion RAS?

- “Can Save GFR”
- 1) Creatinine <4mg/dL or ~350 µg/L
 - 2) Size >9cm
 - 3) Glomeruli seem well-preserved on Bx
 - 4) Function shown on nuclear scan or IVP
 - 5) Retrograde filling by collaterals seen on angiography

What is the impact of pre-op renal function?

- revascularization most beneficial in pts that haven't developed severe, permanent impairment
- revascularization should NOT be recommended if severe azotemia (creat >4mg/dL)
- patients with recent rapid deterioration of renal function have better outcomes after Rx
- occasionally, pts w/ ESRD from IN can benefit from revascularization (B/L complete occlusion + viability due to collaterals) → otherwise ESRD patients don't benefit

What are the 2 most common renal Bx histopathologic features in atherosclerotic RAS?

- 1) **nephrosclerosis (most common)**
- 2) cholesterol emboli

What findings on renal Bx suggest irreversible damage?

- | | | |
|------------------------------------|---|---------------------------------|
| 1) glomerular hyalinization | \ | revascularization should not be |
| 2) extensive atheroembolic disease | / | recommended |

SURGICAL REVASCULARIZATION

Pre-op preparation

What investigations need to be arranged prior to renal revascularization?

- patients with fibrous dysplasia → usually young and healthy
- patients with atherosclerosis → r/o CAD, CVD
→ angioplasty/CABG or CEA/stent prior to Rx

Operative Techniques

What are the indications for total or partial Nx in the setting of RVH or IN?

→ **limited role now**

- 1) severe arteriolar nephrosclerosis
- 2) severe renal atrophy
- 3) uncorrectable renovascular lesions
- 4) renal infarction

What surgical revascularization options are available for RVH?

- if healthy aorta:
 - 1) aortorenal bypass
 - free graft of autologous hypogastric artery or saphenous vein
 - synthetic graft
 - 2) renal endarterectomy
 - 3) extracorporeal microvascular reconstruction + autoTx
- if atherosclerotic aorta:
 - 1) splenorenal bypass (L) → make sure celiac artery is patent
 - 2) hepatorenal bypass (R) → make sure celiac artery is patent
 - 3) iliorenal bypass
 - 4) supraceliac or lower thoracic aorta for renal reconstruction

How successful is surgical revascularization for RAS/RVH?

- cure = BP <140/90
- improvement = reduction of dBp by 10-15 mmHg or normotensive on meds
- **less M&M for patients with FD compared to atherosclerosis** → healthier
- 5 and 10yr survival rates are approximately 90% and 75%, respectively
- failure rate ~10-15% → **failure rate slightly worse for atherosclerosis than FD**
- FD } **50-60% cure**, 30-40% improved, **<10% failed**
- atherosclerosis } 15-45% cure, **50-75% improved**, 5-20% failed

How successful is surgical revascularization for IN?

- 25-55% improve
- 25-50% stable
- 10-20% deterioration

What are the potential complications of renal vascular surgery?

- mortality } minimal in patients with fibrous dysplasia or aneurysm (usually young)
 - } 6-10% in patients with atherosclerotic renal artery disease (older, sicker)
 - } reduced mortality with pre-op correction of CAD or CVD, avoidance of B/L renal surgery, and avoidance of surgery on a diseased aorta
- HTN } common in early post-op period
 - } may persist for several wks after surgery → need to do renal scan to confirm patency
- hemorrhage } usually due to poor surgical technique
 - } late hemorrhage can occur weeks, months, or even yrs after
 - infected suture line
 - rupture of noninfected false aneurysm at anastomotic site
 - erosion of prosthetic graft into GI tract
- renal artery thrombosis } occurs in <5%
 - } usually occurs within first few days post-op and is due to poor technical performance (persistent or sudden HTN & elevated creatinine)
 - } RFs include post-op hypoTN, hypercoagulable state, & hypovolemia
- renal artery stenosis } occurs <10%
 - } late complication
 - } due to faulty sutures, intimal trauma, incomplete excision of primary vascular disease, wide disparity in vessel size, dissection of a distal intimal flap, torsion, angulation, kinking
- renal artery aneurysm } occurs in <10%
 - } more common in kids
 - } may be associated with stenosis distal to aneurysm
 - } more common with use of gonadal vein grafts so these are not used
- aortic complications } aortic thrombosis, distal embolization, etc
 - } aortic dissection from clamping and unclamping
- visceral complications } injuries to spleen, pancreas during alternative bypass techniques
 - } GB necrosis with ligation of R hepatic artery during hepatorenal bypass
- ARF } can be prevented in most cases
 - } avoid warm ischemia >30 minutes

What are the RFs associated with increased mortality after surgical revascularization for RAS?

- 1) bilateral renal revascularization
- 2) concomitant major aortic disease or aortic revascularization
- 3) elevated creatinine (>2 mg/dL or 177mmol/L)
- 4) uncorrected CAD or CVD

What is the management of recurrent RAS?

- failed PTA may increase difficulty or compromise outcome of surgical revascularization
- recurrence after surgical revascularization is usually a late complication
- repeat surgical revascularization is difficult

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

What are the technical aspects of angioplasty?

- need a pre-dilation angiogram & post-dilatation angiogram
- select proper sized balloon catheters → should correspond w/ original diameter of renal artery
- axillary or femoral access + Seldinger technique
- have vascular sx available → in case of inadvertent occlusion or disruption of renal artery

How does PTA work?

- atherosclerotic RAS → **fracture of atherosclerotic plaque is main mechanism**
→ stretching of arterial wall w/ tearing of media & adventitia (minor)
- FD RAS → main mechanism is stretching of arterial wall w/ tearing of media and adventitia

What are the complications of PTA for RAS?

- 1) access related → pseudoaneurysm formation
→ bleeding/arterial injury
- 2) procedure related → transient deterioration of renal fxn (contrast load) } **most common**
→ contrast allergy
→ renal artery thrombosis } Rx with thrombolytic agent or emergency Sx
→ intimal dissection } Rx with stent if large
→ rupture of renal artery } Rx by reinflating balloon then emergency Sx

What can be done to decrease the risk of renal dysfunction from contrast?

- hydration, NaHCO₃, mucomyst
- minimize contrast volume, use low-osmolar contrast
- separating diagnostic angio from PTA by several days
- carbon dioxide studies

Fibrous Dysplasia and RAS

What is the success rate of PTA for FD-related RAS?

→ **PTA is primary modality of choice for FD-related RAS**

- no stents used
- technical success rates ~90%
- improvement or cure of HTN in >80%
- major complication rate ~5%
- re-stenosis rates after moderate f/u ~10% → most cases successfully re-dilated

Atherosclerotic RAS

What is the success rate of PTA for atherosclerotic RAS?

- **PTA for atherosclerotic RAS less successful & assoc'd w/ higher M&M than with FD**
 - patients usually older w/ more comorbidities
 - usually ostial or proximal main renal artery dz } may be extension of aortic disease
 - propensity for atheroembolism
- **use of stent improves outcomes**
- technical success rates ~80% → **worse with ostial disease**
- improvement or cure of HTN ~60% → **worse with bilateral disease**
- major complication rate ~10%
- restenosis rates ~20% → worse with ostial disease
- improvement or stabilization of renal function in ~70%

Inflammatory RAS

What is Takayasu's arteritis?

- inflammatory disease of unknown etiology that affects aorta & its branches
- one of causes of **RAS in children**
- more common in **asian F**
- **PTA should only be performed in the absence of active disease or inflammation**
- technical success rates ~80%
- improvement or cure of HTN in ~90%
- restenosis rates ~20%

Children

What are the causes of RAS in children?

- 1) FD
- 2) middle aortic syndrome
- 3) neurofibromatosis
- 4) Takayasu's arteritis

ENDOVASCULAR STENTING

What is the role of renal artery stents?

- **used mainly for atherosclerotic RAS**
- opposes the elastic recoil force of plaque that makes PTA less successful
- **used especially for ostial lesions } PTA alone less likely to succeed**
- radiopaque, expandable metallic wire mesh tubes → shortens with expansion
- stent should cover entire length of lesion
- for ostial lesions, the stent should protrude 1-2mm into aortic lumen

What are the indications for endovascular stent placement for RAS?

- 1) poor immediate results during PTA } more likely in atherosclerotic RAS
- 2) restenosis after PTA
- 3) arterial dissection or intimal flaps
- 4) primary placement for ostial lesions

How successful are endovascular stents for RAS?

- technical success rates >95%
- **cure of HTN only ~30%** → usually assoc'd w/ essential HTN & renal parenchymal damage
- restenosis rates ~15%
- **improvement or stabilization of renal function in 75%**

What are the RFs for poor outcomes with endovascular stenting?

- 1) baseline renal impairment
- 2) old age (>70yrs)
- 3) DM

What are the complications associated with endovascular stent placement for RAS?

- similar to PTA
- **access related complications more common** } larger arterial puncture needed
- **lower rate of intimal injury and dissection** → stent itself is treatment
- slightly higher contrast load
- rare reports of endovascular infection → can progress to mycotic aneurysms of aorta/renal artery
→ may need major excision and vascular reconstruction
- mortality rates ~3%

OTHER RENAL ARTERY DISEASES

Renal Arterial Aneurysms

What is the epidemiology of renal artery aneurysms?

- localized dilatation due to weakening of elastic tissue and media of wall
- 0.1-0.3% incidence
- majority are small & asymptomatic BUT can be clinically significant:
 - causative relation to HTN
 - associated local symptoms
 - risk of rupture

What are the 4 different types of renal artery aneurysms, according to Poutasse?

- 1) Saccular → **most common type (75%)**
 - occur at bifurcation of renal artery, so **branch involvement is common**
 - 25% bilateral or multiple aneurysms
 - may become involved w/ intramural calcification or atherosclerotic degeneration
 - **may rupture spontaneously**, may erode into renal vein or renal pelvis, and may form mural thrombus +/- emboli
- 2) Fusiform → occurs as **uniform dilatation of entire segment of renal artery**
 - actually a **post-stenotic dilatation**
 - more common in **young HTN'sive patients with FD**
 - **not calcified**
 - may become thrombosed
- 3) Dissecting → usually complication of renal arterial involvement w/ atherosclerosis, intimal or perimedial fibroplasia
 - results from a **tear in the internal elastic membrane of the renal artery**
 - blood flow through opening separates intima from rest of arterial wall
 - may result in **arterial thrombosis + renal infarction or rupture + hemorrhage**
- 4) Intrarenal → of mixed origin } may be congenital, post-traumatic, iatrogenic, neoplastic, or associated with polyarteritis nodosa
 - **usually saccular or fusiform +/- calcification**
 - have a **propensity for rupture**
 - can resolve if post blunt trauma or percutaneous renal Bx

How do renal artery aneurysms present?

- **medial ringlike calcification (in or near renal hilum) on AXR → 50% of cases**
- HTN
- subcostal or flank pain
- hematuria
- abdominal bruit
- palpable pulsating mass (rare)

List causes of renal artery aneurysms }}} “PICK ME MAMA”

- | | | |
|---------------------------------|------------------|------------------------------|
| - Polyarteritis nodosa | - Marfan’s | - Medial FD (microaneurysms) |
| - Iatrogenic (eg PCNL, Bx, PNx) | - Ehler’s Danlos | - Atherosclerosis |
| - Congenital | | - Mycotic (infection) |
| - Kawasaki’s disease | | - AD PCKD |

What are the complications of a renal artery aneurysm?

- peripheral dissection
- arterial thrombosis + renal infarction
- emboli from mural thrombus within aneurysm
- obstructive uropathy
- erosion into a vein + formation of AVF
- spontaneous rupture + hemorrhage

What are the RFs for rupture of a renal artery aneurysm?

- | | |
|---------------------------------------|-------------------|
| 1) absent or incomplete calcification | 3) coexisting HTN |
| 2) size >2cm | 4) pregnancy |

List the indications for surgical removal of renal artery aneurysms }}} “WEBBERRR’S DIC”

- 1) **W**oman of childbearing age who is likely to conceive
- 2) **E**mbolization from thrombus with aneurysm on angio
- 3) **B**igger than >2cm + other RF for rupture
- 4) **B**P uncontrolled
- 5) **E**xpanding on imaging
- 6) **R**enal ischemia
- 7) functionally significant **R**AS
- 8) **R**uptured
- 9) **S**ymptoms (flank pain, hematuria)
- 10) **D**issecting aneurysm
- 11) **I**ncomplete **C**alcification

What are the surgical options for renal artery aneurysms?

- endovascular Rx → embolization of aneurysm without disrupting renal flow
→ placement of arterial stent to exclude aneurysm
- open surgical reconstruction → reanastomosis with Dacron or saphenous
- ex vivo reconstruction for multiple aneurysms
- nephrectomy
- renal autoTx

Renal AVF

What are the 3 types of renal AVFs?

- 1) congenital → 25% of all renal AVFs
→ occur equally in M and F, manifesting late in adult life
→ **cirsoid or angiomatous configuration with multiple communications**
→ usually supplied by renal arterial branch of normal caliber
- 2) idiopathic → 5% of all renal AVFs
→ single communication
- 3) acquired → **most common type at 70%**
→ **single communication**
→ mostly due to renal Bx } others include RCC, renal trauma (blunt/penetrating), inflammation, renal Sx (Nx, PNx, PCNL)

How do renal AVF's usually present?

- depends on size
- **systolic abdominal bruit → 75%**
- CHF, cardiomegaly, diastolic HTN → 50%
- hematuria → 33%
- tachycardia
- palpable flank mass (rare)
- no/minimal affect on CVP

List the indications for surgical mgt of a renal AVF?

- need for Rx depends on cause and associated manifestations } 70% of acquired AVF's from renal Bx close spontaneously w/in 18 months
- CHF
- HTN uncontrolled
- Hematuria
- Expanding lesion on imaging
- Retroperitoneal bleed (ruptured)
- Renal Insufficiency/failure

What are the management options for a renal AVF?

- 1) embolization
- 2) total or partial Nx → mainly for congenital (cirsoid) fistulas

Renal Artery Thrombosis or Embolism

What is the presentation of renal artery thrombosis and embolism?

- thrombosis → proximal or middle third of main renal artery
- embolism → peripheral arterial branches
- both → **acute occlusion more common on L**
 - varied presentation } oliguric ARF if B/L vs unnoticed if chronic progressive occlusion
 - dull abdominal ache or flank pain associated with N/V and fever
 - HTN
 - microscopic hematuria
 - albuminuria
 - elevated serum LDH

What are the causes of renal artery THROMBOSIS (CHART)? } } } “FAT Pig SAT UP”

- 1) **FD of renal artery**
- 2) **Atherosclerosis of aorta or renal artery**
- 3) **Trauma**
- 4) **Polycythemia**
- 5) **Syphilis**
- 6) **Angiography (aortic or renal artery)**
- 7) **Thromboangiitis obliterans**
- 8) **Umbilical artery catheterization in neonates**
- 9) **Polyarteritis**

What are the causes of renal artery EMBOLISM (CHART)? } } } “MAP TO embolism AVE”

- 1) **MI** (acute)
- 2) **A-fib**
- 3) **“Paradoxical” embolism** → presence of ASD/VSD
- 4) **Tumour** (cardiac)
- 5) **Open heart surgery**
- 6) **Aneurysm** } saccular renal artery aneurysm
 } ventricular aneurysm
- 7) **Valvular vegetations** (aseptic)
- 8) **bacterial Endocarditis**

What is the management of renal artery thrombosis/embolism?

- if unilateral → **non-operative Rx with systemic anticoagulation**
 - percutaneous transcatheter thromboembolectomy
 - patients usually have serious underlying extrarenal disease
- if B/L or in a solitary kidney → **renovascular reconstruction**
 - if extensive collaterals seen on angio, consider non-Sx Rx

Neurofibromatosis

What is neurofibromatosis?

- congenital hereditary disorder } young age at presentation
- **vascular abN'ities** affecting kidneys, } thickening of intima
 - heart, and GI tract } proliferation of neural tissue w/in arterial wall
 - } aneurysmal dilatation
 - } perivascular nodular proliferation
- **café-au-lait spots + cutaneous neurofibromas + CNS tumours + skeletal d/o's + Pheochromocytomas**
- **HTN usually due to RAS** → can occasionally be from pheo or coarctation of aorta

What is the management of RAS from neurofibromatosis?

- surgical revascularization is Rx of choice for associated RVH

Middle Aortic Syndrome

What is the middle aortic syndrome?

- rare disorder } occurs in kids & young adults → ?form of Takayasu's arteritis (?autoimmune)
 - characterized by **nonspecific stenosing arteritis affecting aorta + major branches**
→ including renal arteries
- Rx → **renal autoTx is Rx of choice** } inflammatory process **doesn't usually involve iliacs**

Page's Kidney

What is a Page's Kidney?

- kidney **compressed by subcapsular or perirenal process causing renal ischemia**
- induces unilateral hypersecretion of **renin** and contralateral suppression → HTN
- Dx if presence of surrounding hematoma or encasing fibrous pseudocapsule

What are the causes of a Page's kidney?

- 1) blunt trauma
- 2) closed renal Bx
- 3) anticoagulation
- 4) hemorrhage from tumour

What is the management of a Page's kidney?

- aim is to preserve renal function and cure HTN
- medical anti-HTN'sive Rx + observation → sometimes Page's kidney resolves
- percutaneous evacuation of perirenal hematoma
- open drainage of hematoma
- nephrectomy

Extrinsic Obstruction

What are the causes of extrinsic obstruction of the renal artery?

- rare } neural tissue, musculocutaneous fibers, diaphragmatic crura
- } perivascular fibrosis from inflammation, trauma, tumour, radiation

Renal Parenchymal Disease

What are some parenchymal causes of renal HTN?

- chronic pyelonephritis with scarring
- hydro
- congenital hypoplasia or dysplasia
- segmental hypoplasia (Ask-Upmark kidney)
- VUR
- RCC
- benign cysts
- Wilms' tumour
- radiation nephritis
- JG cell tumour

List renovascular diseases that involve the branches of the renal artery. }}} "FAT TAN"

- 1) **FD** } perimedial (most common, others are more proximal), intimal, medial
 - 2) **Arterial aneurysm** } saccular, fusiform, dissecting, intrarenal
 - 3) **Trauma**
 - 4) **Takayasu's arteritis**
 - 5) **AVM** } acquired, congenital, idiopathic
 - 6) **Neurofibromatosis**
- atherosclerosis is rare } usually ostial and proximal main renal artery (usually bilateral)

List renal causes of HTN?

→ benign

- renovascular HTN
- reninoma
- renal parenchymal disease
- Page kidney

→ malignant

- RCC
- Wilm's tumour

List adrenal causes of HTN?

→ benign

- Pheo
- Conn's syndrome (hyperaldosteronism)
- Cushing's
- CAH (11-hydroxylase deficiency) } 21 β -hydroxylase deficiency causes HYPOTN
- adrenal hyperplasia

→ malignant

- adrenal carcinoma
- neuroblastoma

Chapter #37 - Pathophysiology of Urinary Tract Obstruction

GLOBAL RENAL FUNCTIONAL CHANGES

What are the causes of obstructive nephropathy?

Renal

Congenital	Polycystic kidney
	Renal cyst
	Fibrous obstruction at ureteropelvic junction
	Peripelvic cyst
	Aberrant vessel at ureteropelvic junction
Neoplastic	Wilms' tumor
	Renal cell carcinoma
	Transitional cell carcinoma of the renal pelvis
	Multiple myeloma
Inflammatory	Tuberculosis
Metabolic	<i>Echinococcus</i> infection
Miscellaneous	Calculi
	Sloughed papillae
	Trauma
	Renal artery aneurysm

Ureter

Congenital	Stricture
	Ureterocele
	Ureterovesical reflux
	Ureteral valve
	Ectopic kidney
	Retrocaval ureter
	Prune-belly syndrome
	Primary carcinoma of ureter
	Metastatic carcinoma
Neoplastic	Tuberculosis
	Schistosomiasis
	Abscess
	Ureteritis cystica
	Endometriosis
Miscellaneous	Retroperitoneal fibrosis
	Pelvic lipomatosis
	Aortic aneurysm
	Radiation therapy
	Lymphocele
	Trauma
	Urinoma
	Pregnancy

Bladder and Urethra

Congenital	Posterior urethral valve
	Phimosis
	Urethral stricture
	Hypospadias and epispadias
	Hydrocolpos
Neoplastic	Bladder carcinoma
	Prostate carcinoma
	Carcinoma of urethra
	Carcinoma of penis
Inflammatory	Prostatitis
	Paraurethral abscess
Miscellaneous	Benign prostatic hypertrophy
	Neurogenic bladder

What are the main determinants of GFR?

- 1) transglomerular capillary pressure (most important) } afferent/efferent arterioles
- 2) RPF
- 3) glomerular permeability
- 4) oncotic pressure (least important)

Unilateral Ureteric Occlusion (UUO)

Describe the TRIPHASIC response in RBF and ureteral pressure to UUO

- 1) phase 1 (1-2hours) → **↑'d RBF + ↑'d ureteral pressure**
 - stable GFR (tubuloglomerular feedback)
 - early net renal vasodilation from **PGE₂ and NO**
- 2) phase 2 (2-5hours) → **↓'ing RBF + ↑'d ureteral pressure**
 - decreasing GFR
 - short-lived efferent vasoconstriction (mediated by **AT₂, TXA₂, and endothelin**)
 - shift of RBF to inner cortex
- 3) phase 3 (>5hours) → **↓'d RBF + ↓'d ureteral pressure**
 - decreasing GFR
 - from afferent vasoconstriction & decreasing filtration

Bilateral Ureteric Occlusion (BUO)

Describe the BIPHASIC response in RBF and ureteral pressure to BUO

- 1) phase 1 (<1hour) → **mildly ↑'d RBF + ↑↑↑'d ureteral pressure**
 - decreasing GFR
 - only *mild* early vasodilation mediated by **NO, PAF, endothelin**
 - 2a) phase 2a (1-5hours) → **↓'ing RBF + ↑'d ureteral pressure**
 - decreasing GFR
 - prolonged efferent vasoconstriction mediated by **AT₂, TXA₂**
 - RBF *remains in outer cortex* (no shift to inner cortex as with UUO)
 - phase 2b (>5hours) → **↓↓↓'ing RBF + ↑'d ureteral pressure (x24hrs)**
 - decreasing GFR
 - from afferent vasoconstriction & decreasing filtration
- **earlier decrease in RBF } likely related to increased sympathetic output**
→ **ureteral pressure stays elevated } accumulation of vasoactive substances (eg ANP)**
accounts for difference from UUO

What are the findings seen after release of BUO?

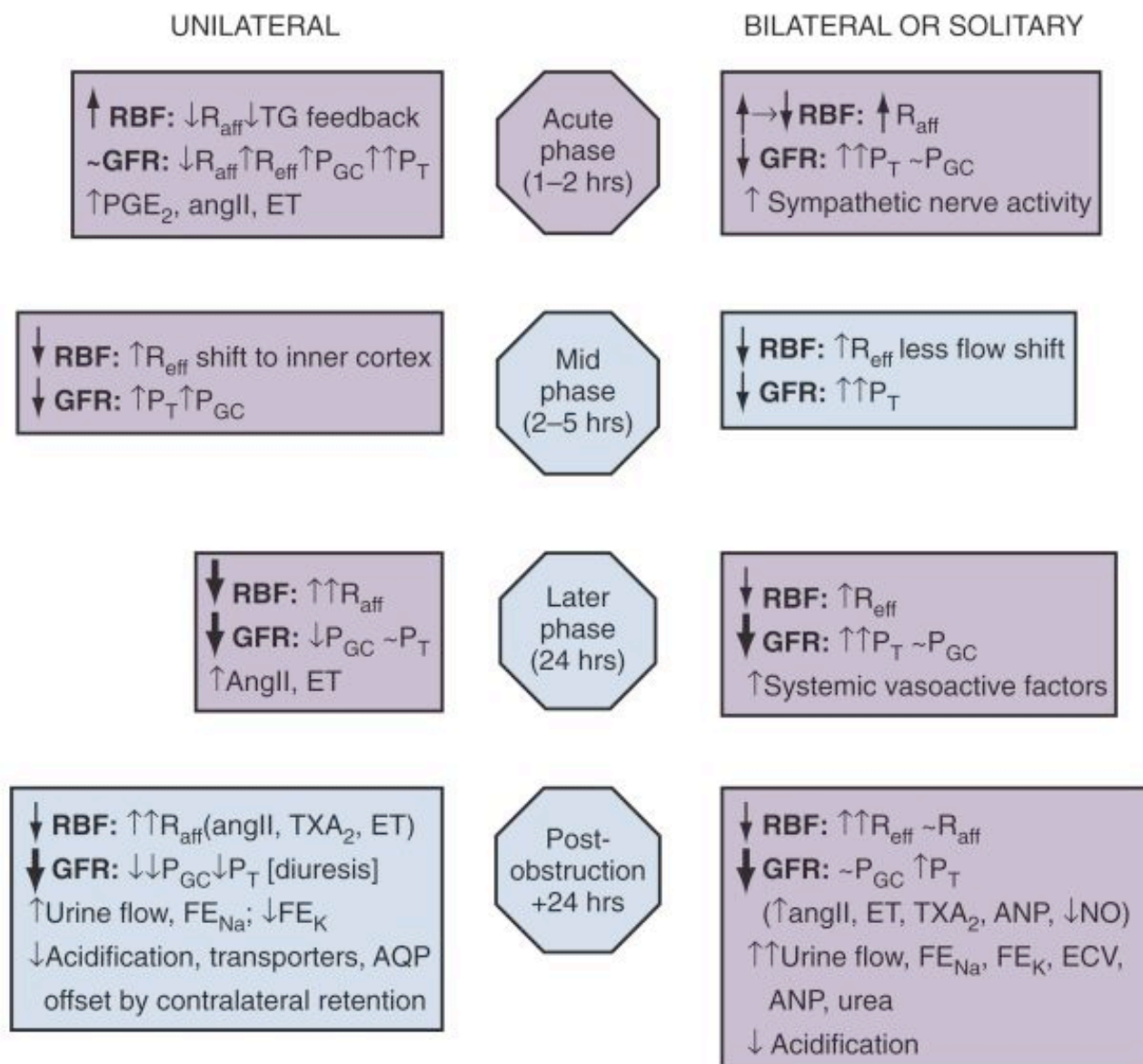
- GFR and RBF remain depressed } due to persistent vasoconstriction of afferent arteriole
- ↑'d urine flow + Na excretion } mediated by expanded volume, osmotic agents (eg urea) & ANP

What factors are responsible for the triphasic response seen with ureteral obstruction?

- 1) **vasoactive substances** made and released at different rates
- 2) physical **damage to the glomerular & tubular units**
- 3) **extra-renal compensatory mechanisms**

What are the effects of obstruction on ureteral function?

- depends on degree & duration of obstruction, rate of urine flow, and presence of infection
- obstructed ureter can't coapt ureteral wall & can't generate N active intraluminal pressures
- 1) increased resting ureteral intraluminal pressure initially
 - ureteral pressure reaches maximum ~3hrs
 - declines afterwards to a little above baseline, then plateaus } remains elevated longer in BUO
 - due to reduced RBF, GFR, pyelovenous reabsorption, etc
 - resting ureteral pressures can't differentiate obstruction from non-obstructive dilation
- gradual increase in ureteral length & diameter \ potential for ↑'d contractility
- also get transient ↑ in amplitude & frequency of peristaltic ctx's / offset by dilated, thin muscle
- ureteral smooth muscle hypertrophy occurs over time
- presence of infection impairs urine transport by decreasing ureteral contractions
- N ureteral peristalsis can occur after relief of obstruction <2wks



→ TRIPHASIC RESPONSE TO URETERAL OBSTRUCTION

Partial Ureteric Occlusion

What is the effect of partial ureteric obstruction on renal function? (dog studies)

- little irreversible damage up to 2 weeks
- minimal recovery of renal function after 8 weeks
- tubular changes mediated by **PGs**, **AT2** (**RAAS activation**)

What is the effect of partial ureteric obstruction in the perinatal period?

- depends on stage of renal development & degree of occlusion
- glomerular/tubular formation may be compromised (irreversible) w/o total loss of kidney fxn

Effects of Obstruction on Tubular Function

What are the general effects of obstruction on renal tubule function?

- 1) lower GFR
- 2) ↓'d urine concentrating ability (decreased urine osmolality)
- 3) increased FE_{Na} → profound in BUO, mild with UUO
*** in acute obstruction, see opposite, increased urine osmolality and decreased FE_{Na} ***

Why is renal urine concentrating ability abnormal after BUO?

→ no significant POD in UUO due to compensating normal contralateral kidney

- 1) loss of active salt reabsorption from ThickAL → mediated by ANP and a reduction in Na transporters (ENaC, Na/K/ATPase, Na/K/2Cl)
- 2) loss of urea backflux from inner medullary CD
- 3) decreased water reabsorption in PCT, ThinAL, and CD → due to down-regulation of aquaporin-2 (poor response to ADH – “nephrogenic DI”)

What renal tubular effects are seen after relief of ureteral obstruction?

- 1) potassium transport
 - UUO → ↓'d K excretion
 - BUO → ↑'d K excretion
- 2) H ion transport and urinary acidification
 - ↓'d H excretion + inability to acidify urine → mainly in distal tubule
- 3) PO_4 transport
 - UUO → ↓'d PO_4 excretion
 - BUO → ↑'d PO_4 excretion
- 4) Mg transport
 - ↑'d Mg excretion
- 5) peptides and proteins
 - ↑'d excretion of monocyte chemoattractant protein1 } marker of tubular damage
 - ↑'d excretion of ALPase, N-acetyl-β-glucosaminidase, etc (PCT enzymes)
 - ↓'d excretion of Tamm-Horsfall protein, EGF
- 6) metabolic control of ion transporters
 - shift from oxidative metabolism to anaerobic respiration
 - ↓'d ATP levels + ↑'d ADP, AMP, and renal lactate-to-pyruvate ratio

What electrolyte abnormalities are commonly seen after BUO (aka POD)?

- acidosis
- hypoNa
- hypoK (can be elevated if impaired renal function)
- hypo PO_4
- hypoMg

What are the effects of partial ureteric obstruction on tubular function?

- ↓'d RBF
- ↓'d CrCl
- ↓'d urine Na and K excretion
- ↓'d urine concentrating ability

What are the cellular & molecular changes seen with ureteral obstruction?

- 1) tubulointerstitial fibrosis → accumulation of extracellular matrix from increased synthesis of tissue inhibitors of metalloproteinases (**TIMPs**)
→ stimulation of inflammatory cytokines (**TGF- β , ATII, NF κ B, & TNF- α**)
- 2) tubular atrophy & apoptosis → obstruction-induced apoptosis starts after day 4
(mediated by **caspases, TNF- α**)
→ glomerular cells are resistant to this type of apoptosis
- 3) interstitial inflammation

What experimental drugs can be used to try to decrease renal fibrosis and functional impairment?

- 1) ACE inhibitors → decreased ATII-mediated fibrosis and apoptosis of renal tubules
- 2) aldosterone antagonist (eg spironolactone) → decreased aldosterone-mediated fibrosis
- 3) downregulation of NO (L-arginine) → decreased NOS-mediated inflammation
- 4) bone morphogenic protein 7 → decreased TGF- β -mediated apoptosis
- 5) hepatocyte growth factor → inhibits TGF- β -mediated apoptosis
- 6) pirfenidone → inhibits collagen synthesis

What are the factors that affect compensatory renal growth in the unobstructed kidney?

- compensatory growth (hyperplastic + hypertrophic) seen in contralateral kidney
- NO increase in # of nephrons or glomeruli
- **mediated by IGF-1**
- 1) age } less compensatory growth seen in older patients
- 2) degree of obstruction } compensatory growth less prominent with partial UUO
- 3) duration of obstruction } more compensatory growth with longer durations of UUO

Describe renal recovery after obstruction?

- usually get **full recovery if <2 weeks of obstruction**
- little to **no recovery after >6 weeks of obstruction**
- the longer the obstruction, the less likely the return to normal GFR
- 2 phases of functional improvement (Jones et al):
 - a) **first 2 weeks → improved tubular function**
 - b) **the next 10 weeks → gradual improvement of GFR**

What are the predictors of renal function recovery after obstruction?

- 1) short duration
 - 2) smaller degree of obstruction
 - 3) greater compliance of collecting system
 - 4) presence of pyelolymphatic backflow
 - 5) younger age
 - 6) no renal cortical thinning
 - 7) normal baseline renal function
- renal scan } **DMSA (cortical) best at predicting renal recovery (cf DTPA and MAG-3)**
 - } DMSA scan better defines functional cortex and is less affected by hydro

PATHOLOGIC CHANGES OF OBSTRUCTION

What are the pathologic changes seen with obstruction after 6 weeks of obstruction?

- 1) gross pathology
 - **pelvicaliectasis**
 - **initially heavier more edematous parenchyma but becomes LIGHTER than contralateral kidney 6 weeks after obstruction**
 - **larger in size**
 - **cystic appearance**
- 2) microscopic pathology
 - lymphatic dilation
 - interstitial edema
 - **widespread glomerular collapse**
 - **tubular atrophy**
 - **interstitial fibrosis**
 - **hyalinization & proliferation of connective tissue in collecting system**
 - macrophage infiltration
 - hemorrhage and necrosis
- 3) EM findings
 - tubular atrophy
 - glomerular collapse
 - renal pelvic smooth muscle atrophy
 - more prominent collagen and elastin in outer cortex and outer medulla (role of TGF- β)

GENERAL ISSUES IN MANAGEMENT OF PATIENTS

What are the indications to urgently relieve obstruction (CHART)?

- 1) unilateral obstruction
 - intractable pain or N/V
 - signs of sepsis
 - high-grade obstruction
- 2) bilateral obstruction
 - same as UUO + the following
 - elevated BUN/creatinine or K+
 - signs & symptoms of uremia
 - signs & symptoms of fluid overload

Imaging

What is the role of U/S in diagnosing obstructive uropathy?

→ **1st line**

- no radiation, no contrast, cheap, safe in pregnancy and kids
- mainly anatomic info only
 - } can assess cortical thickness (chronicity of obstruction)
 - } hydro may not represent obstruction (eg VUR)
 - } obstruction may not have hydro (eg early on, dehydration)
- can add Doppler to assess functional component
 - } elevated RI + hydro may represent high-grade obstruction

How are renal resistive indices calculated?

$$RI = \frac{PSV - EDV}{PSV}$$

PSV = peak systolic velocity
EDV = end diastolic velocity

normal = <0.7

What are the causes of a false –ve or false +ve U/S in the setting of obstruction?

→ false –ve

- acute (prior to development)
- intrarenal collecting system
- dehydration
- misinterpretation of caliectasis as renal cortical cysts
- forniceal rupture

→ false +ve

- capacious extrarenal pelvis
- parapelvic cysts
- VUR
- high urine flow rate
- full bladder/retention

What is the role of IVP in diagnosing obstructive uropathy?

- **old gold standard } anatomic AND functional info**
- requires contrast and radiation
- delayed nephrogram and pyelogram indicates functional abnormality
- delayed images give anatomic info (ie hydro, level of obstruction, ureteral tortuosity)

What are the signs of obstruction on IVP?

→ acute

- delay in calyceal filling
- dilation of collecting system
- nephromegaly
- obstructive nephrogram
- fornix rupture with extravasation of contrast

→ chronic

- ureteral dilation & tortuosity
- parenchymal thinning
- calyceal crescents
- soap-bubble nephrogram
- standing column of contrast

What is the role of retrograde pyelography in diagnosing obstructive uropathy?

- safe with renal insufficiency and contrast allergy
- anatomic info only } may give more detail than other studies

What is the role of antegrade pyelography in diagnosing obstructive uropathy?

- when retrograde pyelography not feasible
- when other imaging studies don't adequately define collecting system or ureteral anatomy

What are the 5 different paths of urine egression in an obstructed kidney?

- 1) forniceal rupture
- 2) pyelosinus
- 3) pyelolymphatic
- 4) pyelovenous
- 5) pyelotubular

What is the Whitaker test?

- measurement of renal pelvic pressure during infusion of saline or contrast into collecting system via NT or perc needle at a fixed rate of 10cc/min
 - collecting system pressure – intravesical pressure = true renal pelvic pressure } N is ~5-10 cm H₂O
 - **intrapelvic pressure <15cm H₂O = normal**
 - **intrapelvic pressure 15-22cm H₂O = indeterminate**
 - **intrapelvic pressure >22cm H₂O = obstruction**
- invasive and often discordant results } limited use

What extrinsic factors affect pressure readings during a Whitaker test?

- needle size
- viscosity of perfusing fluid
- flow rate
- tube length and compliance
- temperature
- presence of catheter/fullness of bladder

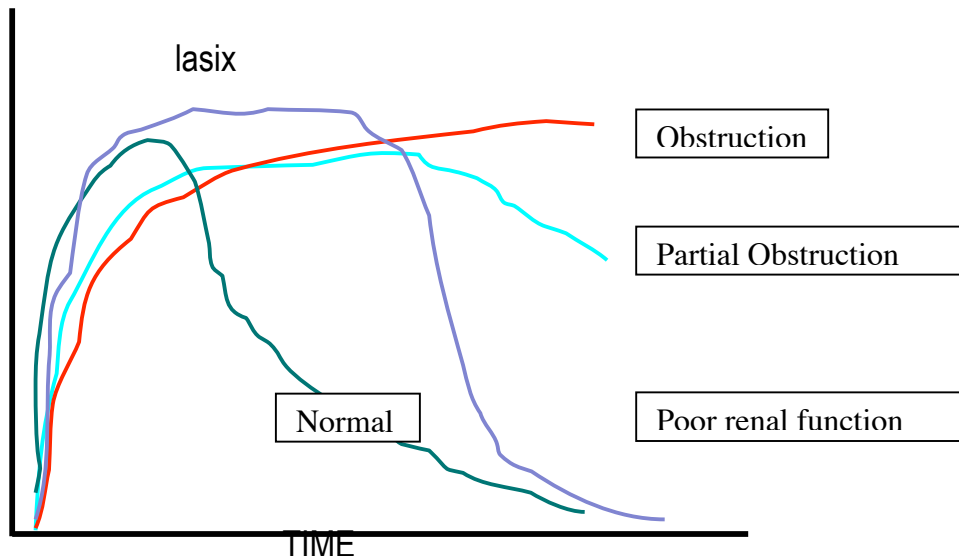
What is the role of nuclear renal scans in diagnosing obstructive uropathy?

- noninvasive, no contrast, no radiation
- radioactive tracers are given iv and used to evaluate functional info } hydrate all patients
 - glomerular tracers (DTPA)
 - tubular tracers (MAG3, orthiodohippurate) } hippurate old but best for effective RBF (EFRB)
 - **cortical tracers (DMSA, glucoheptonate) } no good for UPJO (cortical retention)**
- $T_{1/2} < 10$ minutes = **normal**
- $T_{1/2} > 20$ minutes = **obstruction**
- $T_{1/2}$ 10-20 minutes = **indeterminate**
 - give lasix to produce high-flow and r/o dilated but unobstructed system
 - standard is F+20 study
 - if equivocal, do an F-0 or F-15 study } normalizes partially obstructed-looking curve
 - need to adjust lasix dose to renal function
 - empty bladder prior to renal scan } Foley if can't void

What are the 3 main tracers used for radionuclide renal scans?

- **DTPA** } ~100% filtration >> "glomerular tracer"
 - **good to measure obstruction & best measure of GFR**
 - } 20% extraction coefficient in mature kidney
 - **not as good when kidney function is low or immature**
- **MAG3** } ~100% tubular secretion (in PCT) >> "tubular tracer" (some say 20% filtration)
 - better image quality, more accurate numerical values } **obstruction & GFR**
 - can estimate RPF
 - } higher extraction fraction (50% in mature kidney) with little cortical retention
 - **more accurate when kidney function is poor or immature**
- **DMSA** } 65% secretion + 35% filtration >> "cortical-tubular tracer"
 - **good for assessing parenchyma (scars) and split function**
 - gives information on GFR
 - **no good for UPJO as doesn't give info on drainage } + cortical retention**

What do the nuclear scan curves of an obstructed system look like?



What are the main indications to catheterize prior to a nuclear renal scan?

- 1) suspected LUT obstruction
- 2) VUR
- 3) neurogenic or non-compliant bladder
- 4) low-lying, pelvic kidneys

What are the causes of a falsely delayed renal scan?

- capacious collecting system
- renal insufficiency
- renal immaturity in neonates
- dehydration
- presence of VUR
- elevated intravesical pressure (full bladder, neurogenic bladder, inability to void, etc)
- patient motion

What are the 3 main ways to determine split/differential renal function?

- 1) nuclear renography
- 2) split 24-hr urine creatinine clearance
- 3) split 24-hr urine inulin clearance

What is the role of CT in diagnosing obstructive uropathy?

→ **1st line for suspected ureteral obstruction**

- radiation +/- contrast
- non-contrast spiral CT 97% accurate for ureteral stones } can see stones radiolucent on KUB
- shows more anatomic detail than U/S and IVP
- shows some functional info when used with contrast enhancement

What are the signs suggestive of obstruction on CT?

- ureteral dilation
- perinephric stranding
- perinephric fluid
- nephromegaly

What is the role of MRI in diagnosing obstructive uropathy?

- no radiation or contrast } safe in pregnancy
- can identify hydroureteronephrosis
- CAN'T identify ureteral stones or ureteral anatomy in unobstructed system
→ add lasix to help identify ureteral anatomy in unobstructed system

HTN

What is the risk of HTN with ureteral obstruction?

- volume overload causes HTN in BUO
- UUO not usually associated with HTN
→ good chance of reversal of new-onset HTN with relief of BUO but less likely with UUO

Renal Drainage

Which is better, ureteral stents or NTs?

- most studies show no significant difference in health-related QOL
- stent better in coagulopathic patients
- NTs better in cases of extrinsic obstruction
→ more reliable decompression w/ larger caliber instrument (eg 8Fr pigtail vs 6Fr stent)
→ stent diameter doesn't predict risk of failure

Surgical Intervention

When do you consider Nx over reconstruction for obstructive uropathy?

- drain kidney for at least 6-8 weeks before renal scan
- differential renal function <10-15%
- in patients with renal dysfunction, may want to leave kidney even if <10-15% function
as it may prolong the time until need for dialysis

Pain Management

What are the benefits of using NSAIDs in controlling pain from obstructive uropathy?

- better pain reduction, less need for rescue analgesia & less N/V than narcotics (meta-analysis Holdgate & Pollock 2004)
- NOT for patients with renal insufficiency
- decreased PG-induced pain potentiation
- decreased renal pelvic pressures by decreasing RBF (vasoconstriction of afferent arteriole)
- decreased renal pelvic pressures by up-regulating AQP2 channels

Post-Obstructive Diuresis

Define POD?

→ **urine output >200cc/hr following relief of urinary tract obstruction**

→ usually only with BUO or UUO of solitary kidney

1) **physiologic POD** most common cause

- volume overload (↑'d fluid and ANP)
- solute accumulation (Na, urea)

2) **iatrogenic POD** can also occur

- excessive re-hydration
- use of glucose-containing fluid (osmotic diuresis)

3) **pathologic POD** due to several factors:

a) **loss of active Na reabsorption from ThinAL** } **“salt-wasting nephropathy”**

→ mediated by ANP & ↓'d Na transporters (ENaC, Na/K/ATPase, Na/K/2Cl)

b) **loss of urea backflux from inner medullary CD** } **“medullary washout”**

→ loss of medullary counter-current gradient

c) **decreased H₂O reabsorption in PCT, ThickAL, and CD** } **poor response to ADH**
“nephrogenic DI”

→ mediated by down-regulation of AQP-2 channels

→ pathologic POD usually only occurs in patients with:

- signs of fluid overload (edema, CHF, HTN)
- abnormal renal function
- abnormal electrolytes

What are the RFs for POD?

→ clinical

- chronic obstruction
- HTN
- CHF
- edema
- wt gain
- DM
- uremic encephalopathy

→ laboratory

- azotemia
- hyperK
- hyperPO₄
- hypoCa
- low bicarb (acidosis)

What is the management of POD?

1) N renal function + lytes, no fluid overload, mentally alert and able to drink

→ monitor vitals & U/O

→ D/C home if no POD

→ if POD, continue to drink & monitor VS's + daily lytes, Mg, PO₄, creatinine until POD resolves

2) abN renal fxn or lytes, fluid overload, poor cognitive function or hypovolemic

→ admit and monitor vitals and U/O q2-4h

→ monitor serum lytes (including Mg and PO₄) and serum creatinine q12h or less

→ urine electrolytes (guides replacement fluids) and urine osmolality

→ iv fluids replaced at 1:2 } type of fluid based on urine lytes (start with 1/2 NS)

How can one diagnose GU obstruction? *OSCE*

1) History

→ Acute

- pain } unremitting flank pain +/- radiating to groin or thigh
- N/V
- fever/chills if infected
- anuria (if BUO)

→ Chronic

→ Bilateral

- increase in abdominal girth: complain that pants don't fit
- uremic sx (mental status change, tremors, GIB)
- ankle edema
- malaise
- anorexia
- H/A
- weight gain
- fatigue
- SOB

→ Unilateral

- intermittent flank pain
- flank pain w/ diuresis (Dietl's crisis)
- gross hematuria
- increased U/O (↓'d renal concentrating ability)
- asymptomatic if slow onset (eg MUO)

→ voiding hx

→ PMHx, Meds, allergies

2) Physical exam

→ Vitals (BP, temp)

→ abdominal exam } abdominal mass (rare)

→ signs of volume overload } peripheral edema, pulmonary congestion, HTN

3) Labs

→ urinalysis } hematuria, proteinuria, crystalluria, pyuria, casts

→ urine lytes } elevated urine Na, decreased urine osmolality, decreased urine-to-plasma creatinine ratio } **different w/ acute obstruction → decreased urine Na, increased osmolality**

→ CBC, lytes, Cr, blood gas } increased urea, Cr, K, acidosis

} NB intraperitoneal bladder rupture will increase Cr w/o renal failure

→ cultures } sepsis if infection

4) Imaging

→ US } good first line test

→ Duplex Doppler US + renal RI's

→ IVU

→ Diuretic Renography

→ Whitaker test } pressure < 15cm water not obstructed, >22cm water obstructed, 15-22 equivocal

→ CT/MR } CT w/o contrast more sensitive for ureteric stones than IVU

} CT gives more info on extrinsic causes of obstruction

} CT + contrast gives functional information

} MR urography accurate to dx obstruction, but stones seen poorly

→ indicated in pts w/ renal failure or w/ contrast allergy

→ high cost, longer time to do study, cannot see stones

What are the causes of polyuria?

1) Water diuresis

- decreased ADH
 - ADH inhibitors } α -agonists, EtOH, opioids, Dilantin
 - excessive intake of hypotonic fluid
 - psychogenic polydipsia
- impaired response to ADH
 - nephrogenic DI (“OLD CARP FISH”)
 - obstruction, Lithium, Demeclocycline
 - Ca excess, Ampho B, Renal failure, PCKD
 - Familial X-linked disorder, idiopathic, sickle cell disease, hypoK
 - cold diuresis
- thirst
 - hyperCa
 - hyper-reninemia
 - K depletion
 - organic primary polydipsia
- central DI
 - idiopathic
 - neoplastic, infiltrative, vascular, inflammatory, trauma

2) Solute diuresis

- Nonelectrolyte
 - Urea } metabolic → hypercatabolism, high protein diet
 - } renal disease → POD, diuretic phase of ATN, post-Tx diuresis
 - Glucose } DM, renal glucosuria, D5W infusion
 - Mannitol
 - Glycerol
 - amino acids
- Electrolyte
 - NS infusion or ++ salt intake
 - diuretics
 - increased ANP secretion
 - hypoaldosteronism
 - renal disease } impaired tubular reabsorption
 - salt-losing nephritis
 - POD
 - diuretic phase of ATN
 - post-TX diuresis
 - chronic tubulointerstitial disease

3) Mixed water-solute diuresis

- combined uncontrolled DM and CRF
- POD

SELECTED EXTRINSIC CAUSES OF URETERAL OBSTRUCTION

Retroperitoneal Fibrosis

What is RPF?

- condition in which a predominantly inflammatory mass in the retroperitoneum envelops & potentially obstructs retroperitoneal structures } usually at ~L4/L5 level
- 1 in 200,000 with 3:1 M predominance } 15% present with systemic fibrosis
- mean age of onset is 50yrs
- aka Ormond's disease, periureteritis fibrosa, fibrous retroperitonitis
- gross appearance } fibrous, whitish plaque encasing aorta, IVC, and their major branches, ureters, & other retroperitoneal structures
} may also involve intraperitoneal structures including the GI tract
- 70% are idiopathic while ~10% are associated with underlying malignancy
- **occurs in 2 phases:**
 - **inflammatory phase** } plasma cells, lymphocytes, macrophages, and eosinophils
→ inflammation more intense at margins of mass
} likely an autoimmune response (?leakage of ceroid lipoprotein from atheromatous plaque in aorta)
 - **fibrotic maturation phase** } development of homogeneous fibrous tissue w/ limited cellularity

How does RPF usually present?

- 1) history and physical
 - usually presents with nonspecific signs and symptoms
 - back, abdo, flank pain
 - may also have:
 - wt loss
 - anorexia
 - N/V
 - malaise
 - fever
 - HTN (50%)
 - oliguria/anuria
 - lower limb edema
 - DVT
- 2) lab work
 - **elevated ESR (90% - most common)** } mainly in inflammatory phase
 - anemia
 - high creatinine
 - hypergammaglobulinemia

What are the IVP or U/S findings of RPF?

- **hydronephrosis (98%)** } extrinsic compression + interference of peristalsis
- classic IVP triad } medially deviated ureters (nonspecific) + extrinsic ureteric compression
+ proximal hydroureteronephrosis
- smooth, hypoechoic mass anterior to lumbar or sacral spine

What are the usual CT/MRI findings of RPF?

- modality of choice
- no evidence of primary malignancies + no significant lymphadenopathy
- fibrotic plaque has similar HU as muscle
- contrast enhancement of mass common (esp. in areas of active inflammatory fibrosis)
- symmetric, continuous encasement of aorta and IVC
- can't distinguish from great vessels on non-contrast CT
- hypointense compared to muscle on T1 MRI } better discrimination of soft tissue
} can distinguish from great vessels
} variable GAD enhancement
 - more enhancement in acute phase

What are the causes of RPF?

→ etiology identified in only 30% of cases } malignancy represents 10% of these cases

Drugs

Methysergide
Hydralazine
Reserpine
Haloperidol
LSD
Methyldopa
β Blockers
Ergotamine alkaloids
Phenacetin
Amphetamines

Periarteritis

Aortic or iliac artery aneurysm
Inflammatory response to advanced atherosclerosis
Collagen vascular disease

Infection

Gonorrhea
Tuberculosis
Chronic UTI
Syphilis

Chemicals

Avitene
Methyl methacrylate
Talcum powder

Radiation Injury

Other

Sarcoidosis
Biliary tract disease
Endometriosis

Retroperitoneal Tumors

Inflammatory Processes

Ascending lymphangitis
Chronic inflammatory bowel disease

Hemorrhage

Abdominal and pelvic surgery
Ruptured viscera
Henoch-Schönlein purpura with hemorrhage

→ “RP TIMBIITS” } Radiation
Periarteritis (eg AAA)
Trauma
Infection (eg syphilis, TB, gonorrhea, etc)
Meds
Biliary disease
Iatrogenic
Inflammatory (eg IBD)
Tumours (eg lymphoma)
Sarcoidosis

List medications that can cause RPF? }}} “PBL HHAMMER”

- | | |
|--------------|----------------|
| - Phenacetin | - Hydralazine |
| - β-blockers | - Haldol |
| - LSD | - Amphetamines |
| | - Methysergide |
| | - Methyldopa |
| | - Ergots |
| | - Reserpine |

What is the management of RPF?

1) ACUTE MANAGEMENT

- preservation of renal fxn } prompt decompression with NT or JJ stent
 - usually JJ stent goes easily
- } monitor for post-obstructive diuresis
- r/o DVT if lower limb edema
- r/o malignancies } hx of Ca, lymphadenopathy, non-classic imaging findings
- stop any possible offending meds } spontaneous resolution rare but reported

2) MEDICAL MANAGEMENT (“STAMP-C”)

- **Steroids** } r/o malignancy prior to initiating Rx
 - } prednisolone 20-60mg PO q2days x 6-8wks, then tapered down to 5mg PO OD
 - regression seen up to ~2yrs
 - **consider H2 blockers and Ca supplements** to decrease side effects of high dose steroids
 - } those w/ systemic manifestations or lab evidence of active inflammation tend to respond better
- **Tamoxifen** } anti-estrogen effects on fibrous tissue (?exact mechanism of action)
 - } 20mg PO OD x 12 months (monotherapy)
 - can also be taken after steroid Rx
 - mainly used after failure of trial of steroids
- immunosuppressants } used in combo with steroids or as monotherapy
 - } AZT (2.5mg/kg PO OD x 3-6mos, then 1.5mg/kg PO OD x 6mos)
 - } Cyclophosphamide (2mg/kg po OD x 3mos, then taper off by 6 mos)
 - } Penicillamine & MMF have also been used

3) SURGICAL MANAGEMENT

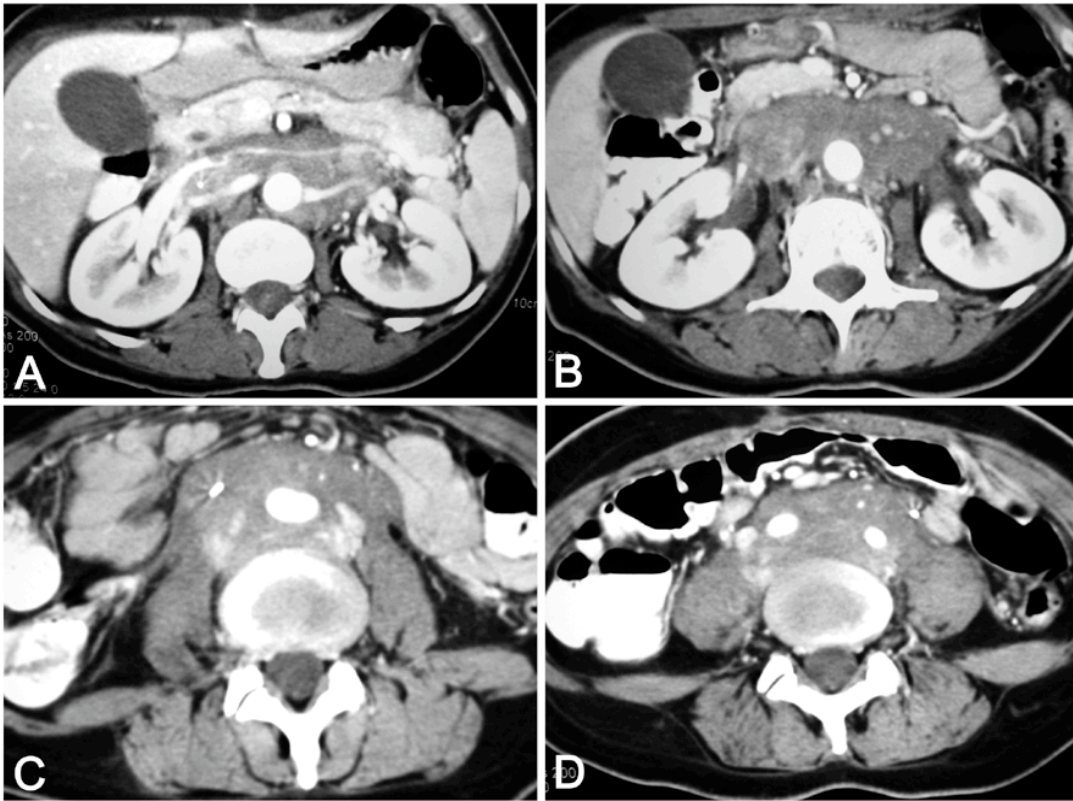
- 2nd line therapy, after trial of medical management
 - always consider treatment of both ureters, even if disease involves 1 ureter
 - open Bx +/- ureterolysis } deep Bx sent for frozen and permanent sections
 - } start dissection at distal non-dilated ureter
 - avoid injury to thin dilated proximal segment (strictures & urine leak/fistulae)
 - } mobilize ureter off mass, then reposition + protect ureters
 - retract laterally + secure peritoneum medially
 - displace anteriorly into peritoneal cavity & close peritoneum behind
 - wrap in omentum or PTFE
 - } consider post-op steroids to decrease recurrence
 - laparoscopic Bx +/- ureterolysis } less morbid operation
 - } can be a tough dissection (~15% conversion rate)
 - other procedures } excision + reanastomosis, Boari flap, ileal ureter, auto-Tx, Nx
- **long term f/u after medical or surgical therapy is essential**
- 1) renal fxn
 - 2) findings suggestive of malignancy
 - 3) recurrence or progression

List optimal management for AAA associated with RPF. **(AUA UPDATE #3 - 2005)**

- 1) AAA repair + ureterolysis } normalized renal function in 75%
- 2) endovascular repair (EVAR) alone } can resolve RPF in many patients

What are the potential complications of ureterolysis for RPF? **(AUA UPDATE #3 - 2005)**

- **ureteric injury (most common)**
- urine leak
- ureteral strictures
- bowel obstruction } more common if omental wrap performed
- bowel injury
- bleeding
- infection



→ CT SCAN OF RPF

What is multifocal fibrosclerosis syndrome?

- syndrome characterized by fibrosis involving multiple organ systems
- idiopathic RPF
- sclerosing mediastinitis
- sclerosing cholangitis
- orbital pseudotumour
- Riedel's thyroiditis

What other diseases are associated with RPF? }}} "M JAWS"

- immune issue
- **M**embranous glomerulonephritis
- **J**RA (kids)
- **A**nkylating spondylitis
- **W**egener's granulomatosis
- **S**LE (kids)

Pelvic Lipomatosis

What is pelvic lipomatosis?

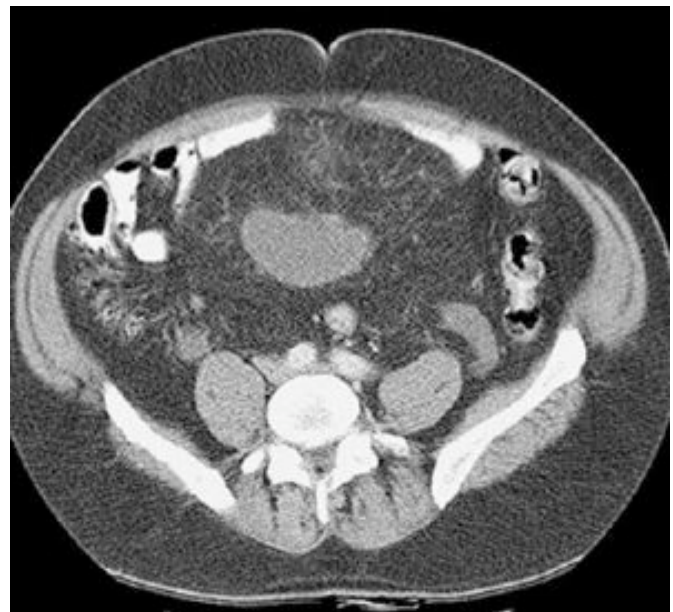
- rare, benign condition marked by pelvic overgrowth of non-malignant but infiltrative adipose tissue
- perivesical and perirectal spaces involved
- mean age at presentation is 48yrs
- more common in **blacks** (2/3 of cases) and mostly in **males** (~20-fold)
- associated with **obesity** but unknown etiology } may be related to abN HMGA proteins
- 35-75% have **HTN**
- usually presents with **LUTS (50%)** or constipation (25%)
 - mostly nonspecific
- may feel suprapubic mass, high-riding prostate, indistinct pelvic mass
- can rarely present with DVT or PE
- ~6% develop renal failure due to obstruction

What are the radiologic findings suggestive of pelvic lipomatosis? (**includes AUA Update #11 – 2008**)

- KUB
 - increased pelvic lucency
- IVP
 - pear-shaped bladder with surrounding pelvic lucency
 - elevated bladder base
 - medial deviation of ureters
 - hydroureteronephrosis (found in 1/3)
- CT (**Diagnostic modality of choice**)
 - increased pelvic fat
 - extrinsic compression of bladder and rectum
 - R/O liposarcoma if there is heterogeneously enhancing regions of fat
- VCUG
 - elongated posterior prostate
 - anterior displacement & elevation of bladder



→ IVP OF PELVIC LIPOMATOSIS
- pear-shaped bladder + pelvic lucency



→ CT OF PELVIC LIPOMATOSIS
- increased pelvic fat

What are the causes of a pear-shaped bladder?

- “U CAN Have Pelvic PEAR”
- **U**rinoma
- **C**ement extrusion from THR
- **A**neurysm (common iliac artery)
- **N**eoplasm (liposarcoma, lymphoma, etc)
- **H**ematoma
- **P**elvic lipomatosis
- **P**soas hypertrophy
- **E**dema
- **A**bscess
- **R**adiation fibrosis

What is the management of pelvic lipomatosis?

- 1) evaluation
 - cystoscopy } consider Bx in all patients, even if asymptomatic
 - cystitis cystica
 - **cystitis glandularis found in 40%**
 - surveillance if found } risk of **adenocarcinoma of bladder**
 - } rigid cystoscopy may be difficult due to elongation of prostatic urethra, high BN, & fixed pelvis
 - consider Bx of tissue if suspicious for liposarcoma (linear areas of increased attenuation)
- 2) treatment
 - weight loss (controversial)
 - NOT EFFECTIVE } steroids, Abx, RADs
 - long term f/u is mandated } risk of progressive ureteral obstruction & risk of bladder adenocarcinoma
 - ureteral stenting
 - percutaneous NT
 - ureteral reimplantation
 - urinary diversion
 - surgical removal of fat or any other pelvic surgery VERY HARD
 - obliteration of surgical planes
 - increased vascularity within fatty mass
 - TURP also difficult due to elongated urethra
 - may need perineal urethrostomy

List conditions associated with pelvic lipomatosis. (AUA Update #11 - 2008)

- “Weber’s Big Dick ROCS Vaginas”
- Weber-Christian disease
- Black
- Dercum’s disease (adiposis dolorosa)
- Retractable mesenteritis
- Obesity
- Cystitis glandularis
- Sclerosing lipogranulomatosis
- Venous obstruction (chronic)

Obstetrics and Gynecologic

How common is hydronephrosis during pregnancy?

- found in 40-100% of pregnancies
 - degree of hydro increases with time } 15% in T1, 20% in T2, ~**90% in T3**
- more common during first pregnancy
- more common on R side } engorged uterine vein, derotated gravid uterus
 - } L side protected from compression by sigmoid
- usually resolves within 6 weeks post-partum
- usually clinically silent } can develop flank pain, pyelonephritis, and renal failure
- hormonal (progesterone) and mechanical (uterus) etiologies theorized

What are the typical findings of gestational hydronephrosis on imaging studies?

- U/S } hydronephroureterosis down to level of pelvic brim (if lower, think stone)
 - } Doppler U/S can look for ureteric jets
- MRI } can see filling defects within distal ureter
 - } can also r/o appendicitis, ovarian torsion, adrenal hemorrhage

What is the management of symptomatic hydronephrosis of pregnancy?

- conservative mgt for most } iv fluids, analgesics, Abx (as needed)
- may need ureteral stent or NT placement
 - rapid encrustation of stents during pregnancy from increased urine Ca excretion

Which Abx's are contraindicated during pregnancy?

- sulfonamides during T1 and T3 } neural tube defects, kernicterus hemolysis (G6PD)
- nitrofurantoin during T3 } hemolysis (G6PD)
- aminoglycosides } CNS toxicity, ototoxicity
- tetracycline } discoloration of teeth, inhibition of bone growth
- chloramphenicol } gray baby syndrome
- TMP-SMX } neural tube defects
- quinolones } abN bone/cartilage growth
- INH } neuropathy, seizures

Benign Pelvic Abnormalities

What are some other benign pelvic conditions that can cause extrinsic ureteral compression?

- tubo-ovarian abscess → occurs in **15% of women with PID**
 - may need NT or stent for high-grade obstruction or urosepsis
 - Rx – ureteral obstruction may resolve w/ ABx or transvaginal drainage
 - open or lap excision of abscess may be needed
 - f/u imaging required to r/o persistent obstruction/scarring/strictures
- endometriosis → usually involves the **bladder** (80%) but ureter is involved in ~15-20%
 - usually **extrinsic** involvement but can also be intrinsic
 - usually involves **distal ureter** } **more common on L side**
 - **ureterosacral ligament most common site of ureteric obstruction**
 - most w/ ureteral endometriosis are asymptomatic } up to 1/3 result in loss of kidney
 - Rx – OCP/Lupron if N renal fxn, minimal hydro, & no fxn'l obstruction on renal scan
 - ureterolysis for extrinsic compression
 - distal ureterectomy + reimplantation for intrinsic disease
- ovarian remnants → syndrome results from incomplete BSO } becomes functional and cystic
 - extrinsic ureteral obstruction from mass effect or a localized fibrosis
 - Rx – surgical excision of mass + ureterolysis
 - leuprolide for poor surgical candidates
- mass lesions of the uterus & ovaries → extrinsic ureteral compression from **uterine fibroids, ovarian cysts, ovarian fibromas**

How can one diagnose ureteral injury?

- 1) intra-op recognition
 - direct recognition
 - inject 1-2cc methylene blue into renal pelvis
 - iv methylene blue
 - look for clear fluid welling up
 - cystotomy or ureterotomy and pass catheter
- 2) post-op recognition
 - flank or abdo pain +/- peritonitis
 - hematuria
 - urine drainage from vagina or wound
 - prolonged ileus or N/V
 - anuria
 - persistent fever, leukocytosis
 - hydronephrosis
 - ureter on path report
- 3) imaging
 - IVP (one-shot) → may miss significant # of injuries
 - CT urogram
 - retrograde
 - antegrade

Why is ureteral injury common during surgical management of endometriosis?

- 1) unrecognized ureteral involvement (15-20%)
- 2) medial deviation of ureter
- 3) difficult visualization } intraperitoneal adhesions from long standing endometriosis

Where is the most common location for ureteral injury during gyne OR?

- **pelvic brim } where it crosses uterine and ovarian arteries (ureter goes under)**
- may get ligation, transection, crush, ischemia, or excision or portion of ureter

What are the RFs for ureteral injury intra-op?

- previous pelvic surgery
- operating at the pelvic brim
- distorted pelvic anatomy on sidewall
- removal of ovarian Ca, abscess, or endometriosis
- repair of bladder injuries
- repair of AAA

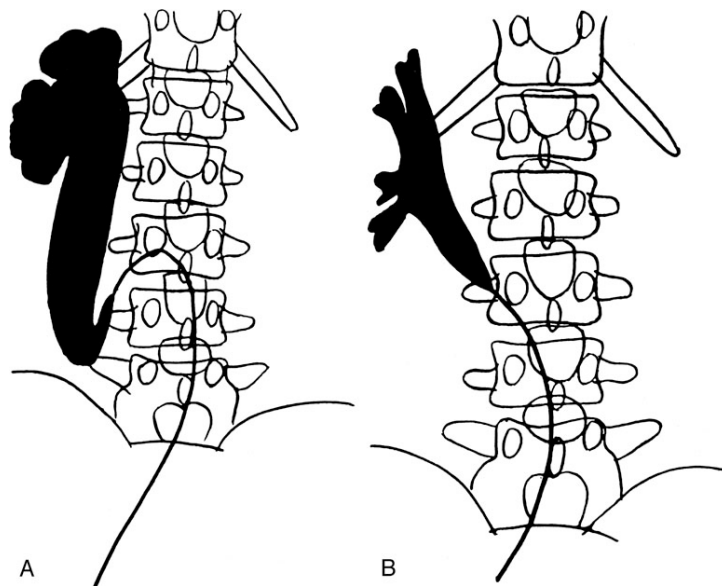
Vascular Causes of Ureteral Obstruction

What are some arterial causes of ureteral obstruction?

- 1) AAA
 - extrinsic compression from mass effect or localized inflammation
 - can see lateral or medial deviation of ureters
 - **obstruction usually associated with medial deviation of ureters**
 - especially with inflammatory AAAs (only 10% of AAAs)
 - Rx – stent insertion
 - open AAA repair resolves obstruction in ~80% (cf 50% with endovascular repair)
 - f/u imaging for recurrent or de novo obstruction
- 2) iliac artery aneurysms
 - suspect iliac artery aneurysm if pulsatile mass on DRE
 - extrinsic compression from mass effect or localized inflammation
 - 35% w/ **common iliac artery aneurysm**; 20% with **internal iliac artery aneurysm**
 - Rx – ureteral stent insertion; removed 6-8 weeks post
 - for common iliac } ureterolysis OR resection of aneurysm + graft OR endovascular graft placement
 - for internal iliac } open surgical ligation + ureterolysis OR endovascular graft
- 3) retroiliac ureter
 - need to look for other associated anomalies
 - Rx – transection of ureter and transposition to normal anterior position
- 4) post-graft placement
 - ureteral obstruction found in **10-20% of patients after AAA repair**
 - usually present in 1st post-op yr
 - from graft placement anterior to ureter, ureteral entrapment in perigraft fibrosis, ureteral devascularization, unidentified ureteral ligation, ureteral compression from post-op pseudoaneurysm
 - Rx – conservative management of early hydronephrosis without renal dysfunction
 - most resolve spontaneously } may need temporary NT or stent
 - trial of steroids or tamoxifen if from perigraft fibrosis
 - transposition of graft, rather than ureter (due to risk of infection), if graft anterior
 - ureterolysis, ileal ureter substitution, chronic ureteral stenting

What are some venous causes of ureteral obstruction?

- 1) puerperal ovarian vein thrombophlebitis
 - **post-partum condition (2-3 days post-partum)**
 - more common on R side
 - abdo/flank pain, fever, and tender, indurated adnexal mass (50%)
 - Rx – conservative therapy with ABx
 - stent as needed
 - lap or open ureterolysis + ovarian vein resection if no resolution
- 2) testicular vein thrombophlebitis
 - reported on the L side
 - Rx – ureterolysis + excision of thrombosed vein
- 3) retrocaval or circumcaval ureter
 - **actually a congenital abnormality in the development of the IVC**
 - **failure of SUPRAcardinal vein to develop into infrarenal IVC**
 - **persistence of posterior cardinal/SUBcardinal veins**
 - 1 in 1100 and 3x more common in M
 - average age at presentation is 20's and 30's } abdo/flank pain, recurrent UTIs, HTN
 - **not always associated with ureteral obstruction** } usually on R side
 - **type 1 (S-shaped fish hook ureter)** and **type 2 (sickle-shaped ureter)**
 - type 1 usually associated with greater degree of hydro
 - type 2 usually crosses at UPJ and so can be confused with UPJO
 - Rx – indicated only if obstruction is present
 - transection and then spatulated UU } open or lap



What other anomalies are associated with a retroiliac ureter?

- renal hypoplasia
- ureteral ectopia
- VUR
- ectopic vas deferens
- hypospadias
- bifid scrotum
- hypoplastic or duplex uterus
- hydrometrocolpos

Chapter #38 – Management of Upper Tract Obstruction

UPJ OBSTRUCTION

What are the causes of UPJO?

- 1) congenital
 - intrinsic
 - aperistaltic segment of ureter } N spiral smooth muscle replaced by abN longitudinal muscle bundles or fibrous tissue
 - true congenital stricture } excess collagen deposition
 - congenital kinks or valvular mucosal folds } mucosa & smooth muscle
 - eg Ostling's folds (valvular mucosal folds) are due to differential growth rates of ureter and body of child (**not obstructive ... disappear w/ linear growth**)
 - extrinsic
 - crossing vessels } LP vessel (truly aberrant if crosses ureter posteriorly)
 - external bands or adhesions
 - persistent fetal convolutions
- 2) acquired
 - stone disease
 - urothelial malignancy
 - post-op/iatrogenic scarring or ischemia
 - inflammatory stricture
 - benign upper ureteral fibroepithelial polyps
 - VUR

What is the significance of aberrant crossing vessels?

- present in ~40% of UPJ obstructions (only ~20% in normal kidneys)
 - can have truly aberrant LP vessel that crosses ureter posteriorly
- may not be the primary cause of obstruction
- whether true cause of UPJ obstruction, presence of crossing vessel has detrimental effect on success rates of minimally invasive treatments of UPJO (eg endopyelotomy)

How does UPJ obstruction present?

- hydronephrosis on perinatal imaging
- flank mass in neonate
- during work-up for azotemia
- intermittent abdo or flank pain (eg Deitl's crisis)
- hematuria
- recurrent UTIs/pyelonephritis
- HTN

What are the imaging modalities used to assess UPJ obstruction?

- **goal is to determine anatomic site and functional significance of obstruction**
- IVP } traditional 1st line test
 - } delay in function, dilated pelvicalyceal system, normal caliber ureter (if seen)
- U/S } often 1st line also (esp for neonates or pregnancy)
- CT urogram } now the most common initial imaging modality
- renal nuclear scan } gives quantitative data on differential renal function and obstruction, even in hydronephrotic renal units (DTPA, MAG-3)
- retrograde pyelography } confirms Dx and gives info on site and nature of obstruction

What are the indications for intervention in UPJO? } “BRUSSSHH”

- **B**ilateral disease
- **R**enal function impairment } overall (<40% w/ poor washout) OR ↓'ing on serial studies
- **U**TIs
- **S**olitary kidney
- **S**ymptoms
- **S**tones
- **H**ydroureterosis ↑'ing on serial studies (eg APD >50mm)
- **H**TN (causal)

What are the management options for UPJ obstruction?

→ **goal is relief of symptoms & preservation or improvement of renal function**

- 1) careful observation with routine reassessment
- 2) open pyeloplasty → gold standard
→ 95% success rate
- 3) laparoscopic pyeloplasty → in good hands, similar to open pyeloplasty
→ ~95% success rate
- 4) endopyelotomy → reduced morbidity but success rate ~85%
→ antegrade or retrograde approach } antegrade slightly better success
→ modality – cold knife, laser, and hot-wire balloon (75% success rate)
→ usually lateral incision; anterior/posterior incision if high-inserting ureter
→ not as successful for high grade obstruction or crossing vessel
- 5) ureterocalycostomy → salvage
- 6) Nx (differential function <12-15%)
- 7) chronic NTs or stents

What is the management of UPJO if endopyelotomy is the treatment of choice?

- 1) evaluation
 - history and physical (coagulopathy, RFs for acquired UPJO)
 - bloodwork (CBC, lytes, creatinine, coags)
 - imaging (retrograde, IVP, U/S, renal scan)
 - urine tests } r/o infection
- 2) endopyelotomy
 - antegrade or retrograde } cold knife, laser, hot-wire balloon
 - if present, stones treated first } don't want extravasation of stones
 - guide wire across UPJ at all times } some advocate placement of stent before cutting
 - full thickness incision from lumen out to peripelvic & periureteral fat
- 3) post-op
 - stent left for 2-4 weeks } 14/7 Fr endopyelotomy stent
 - Hx and P/E, renal scan, creatinine at 1 month, 6months, 12months, yearly x 3yrs

What are the RFs for failure of endopyelotomy?

- stricture >2cm
- obliterated UPJO
- severe hydro
- severe periureteral fibrosis
- untreated infection
- crossing vessel
- poor renal function
- stent migration/obstruction

Antegrade endopyelotomy

What are the indications for offering percutaneous endopyelotomy for UPJO?

- 1) primary therapy for UPJO
- 2) failed open or lap pyeloplasty
- 3) patients with concomitant stones
- 4) patient wishes

What are the contraindications to a percutaneous endopyelotomy?

- 1) long segment of obstruction (>2cm)
- 2) active infection
- 3) untreated coagulopathy
- crossing vessel only a RELATIVE contraindication

What are the options if percutaneous endopyelotomy fails?

- retrograde endopyelotomy
- repeat percutaneous endopyelotomy → NOT recommended if crossing vessel is found
- lap or open pyeloplasty

What are the complications of percutaneous endopyelotomy?

- hemorrhage → slightly higher risk than for usual perc access due to thinner parenchyma often seen in setting of UPJO
- infection
- bowel injury
- urinary leak
- pulmonary complications
- failed endopyelotomy

Retrograde endopyelotomy

What are the contraindications to hot-wire balloon endopyelotomy?

- 1) greater than 2cm obstruction
- 2) presence of stones
- crossing vessel is only a RELATIVE contraindication

What are the advantages of ureteroscopic endopyelotomy over hot-wire balloon endopyelotomy?

- 1) allows direct visualization of UPJ
- 2) cheaper

What are the contraindications to ureteroscopic endopyelotomy?

- absolute
 - 1) long segment of obstruction (> 2cm)
 - 2) active infection
 - 3) presence of stones
- relative
 - 3) presence of significant hydronephrosis } antegrade approach better
 - 4) crossing vessel

What are the complications of retrograde endopyelotomy?

- hemorrhage → crossing vessel
- infection
- ureteral strictures
- urinary leak
- stent migration
- failure of endopyelotomy

Open surgery for UPJO

What are the indications for pre-op decompression of UPJO?

- infection + UPJO
- renal failure from bilateral UPJO or in a solitary kidney
- severe, unrelenting pain

What are the benefits of leaving a post-op ureteral stent?

- decreased urinary extravasation → less risk of fibrosis
- earlier removal of external drains

What are the goals of open pyeloplasty?

- 1) widely patent, tension-free watertight anastomosis
- 2) funnel-shaped transition between pelvis and ureter
- 3) ureter in a position of dependent drainage

What are the different types of open pyeloplasty?

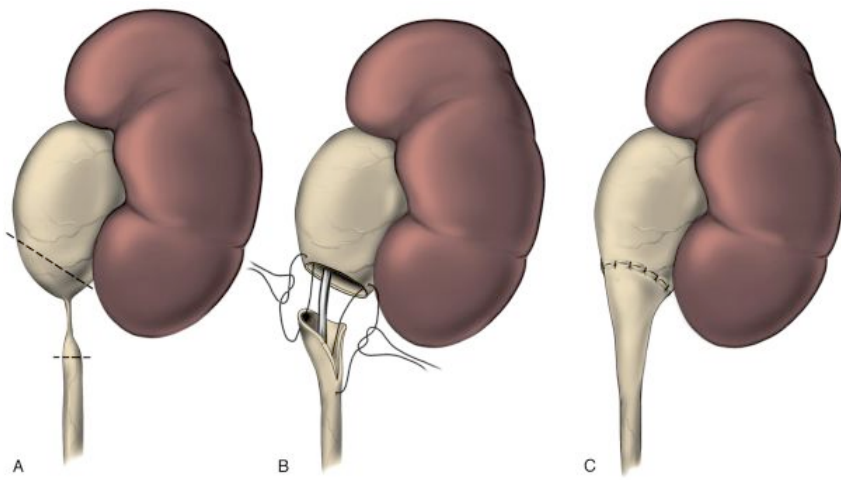
- 1) **dismembered pyeloplasty → 95% success rate**
- 2) Flap procedures } not if crossing vessel (requires transposition)
 - Foley YV-plasty
 - **Culp-DeWeerd Spiral Flap**
 - Scardino-Prince Vertical Flap
 - Fenger-plasty (Heineke-Mikulicz)
- 3) intubated ureterotomy
- 4) **ureterocalycostomy**
- 5) angiopexy (Hellstrom)

When would a dismembered pyeloplasty be preferred?

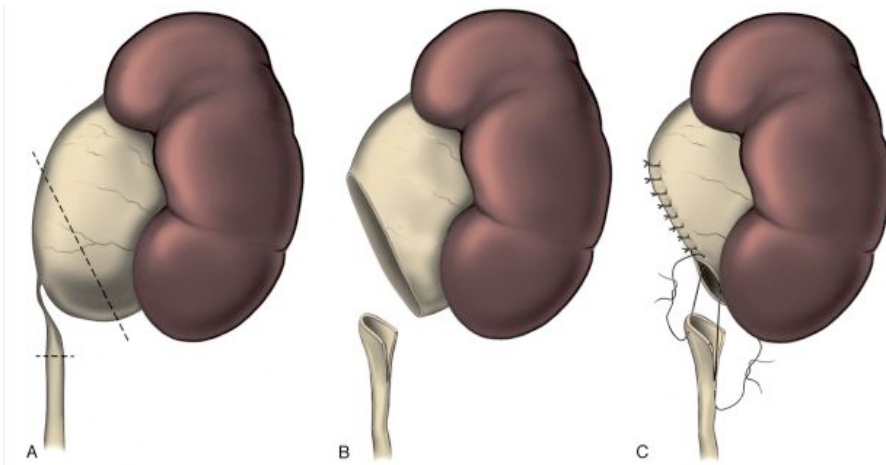
- most cases → allows reduction of redundant pelvis
 - allows straightening of a tortuous proximal ureter
 - can be used regardless of whether ureter inserts high or not
 - only way to completely excise anatomically/functionally abN UPJ
- crossing vessel → allows transposition of the UPJ

When would a dismembered pyeloplasty NOT be recommended?

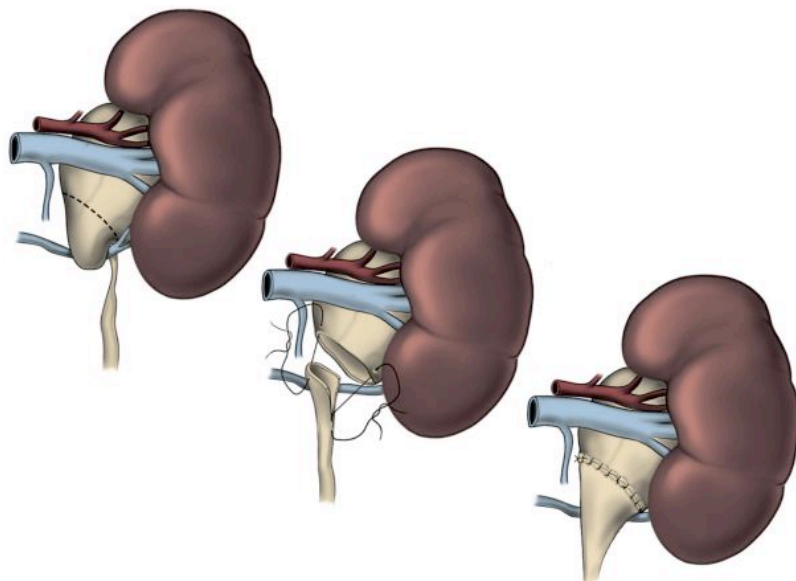
- UPJO associated with lengthy or multiple proximal ureteric strictures
- UPJO associated with a small, inaccessible intrarenal pelvis



→ DISMEMBERED PYELOPLASTY



→ REDUCTION DISMEMBERED PYELOPLASTY (Anderson-Hynes)



→ DISMEMBERED PYELOPLASTY ALLOWS FOR TRANSPOSITION

Describe the technique of a dismembered pyeloplasty (Anderson-Hynes).

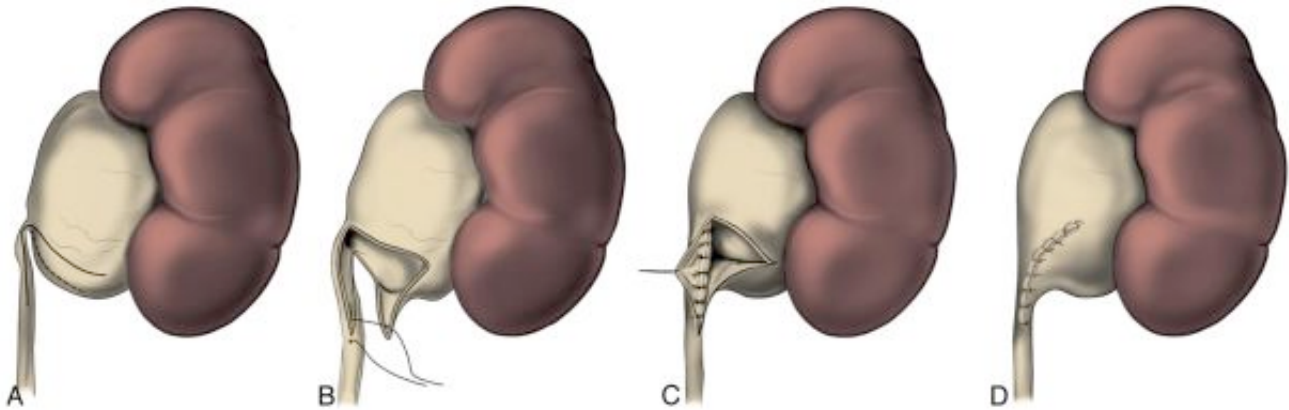
- Pre-op
 - History and P/E
 - lab work: CBC, lytes, Cr, PT/INR, urine tests (r/o infection)
 - investigations: CXR, ECG, other imaging
 - **retrograde pyelogram: r/o concomitant UVJO**
 - stop ASA/Coumadin
 - consent
 - consults: anaesthesia, medicine
 - incision choice
 - do not use dorsal lumbotomy if abnormal retrograde or in muscular youth
- Procedure
 - anterior subcostal incision: muscle splitting
 - sweep peritoneum medially
 - identify Gerota's fascia, which is incised posteriorly over lateral aspect of kidney
 - renal pelvis identified by medial retraction of peritoneal and lateral traction on kidney
 - decompress renal pelvis w/ needle if needed
 - traction suture in renal pelvis to minimize handling
 - dissect out UPJ, traction suture superiorly
 - confirm ureteral length, transect ureter at UPJ
 - mobilize kidney if needed
 - ureter spatulated opposite to traction suture
 - excise redundant pelvis } diamond shaped segment within traction sutures
 - better to leave too much renal pelvis than too little
 - ureter and renal pelvis aligned
 - place NT if necessary
 - anastomosis of ureter to neo-UPJ
 - irrigate renal pelvis free of blood clot
 - place ureteral stent
 - place drain
 - return kidney to native position
 - close fascia
 - place Foley
- Post-op
 - nephrostogram 14d postop
 - stent x 6-8 weeks, U/S at 6 weeks
 - renal scan 1 year post-op
 - imaging at 3 yrs

When would a Foley YV-plasty be preferred?

- UPJO due to a high-inserting ureter } now generally replaced by dismembered pyeloplasty

When would a Foley YV-plasty NOT be recommended?

- crossing vessel
- redundant renal pelvis



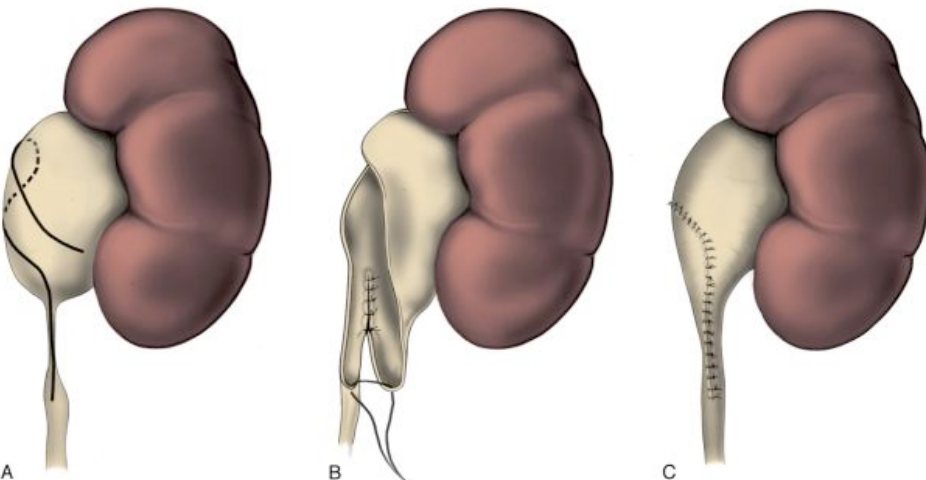
→ FOLEY YV-PLASTY

When would a Culp-DeWeerd Spiral Flap be preferred?

- best suited for large, readily accessible extrarenal pelves with ureter inserting in an already dependent, oblique position
- **preferred over dismembered pyeloplasty when there is a long segment of proximal ureteral narrowing or stricture**

When would a spiral flap NOT be recommended?

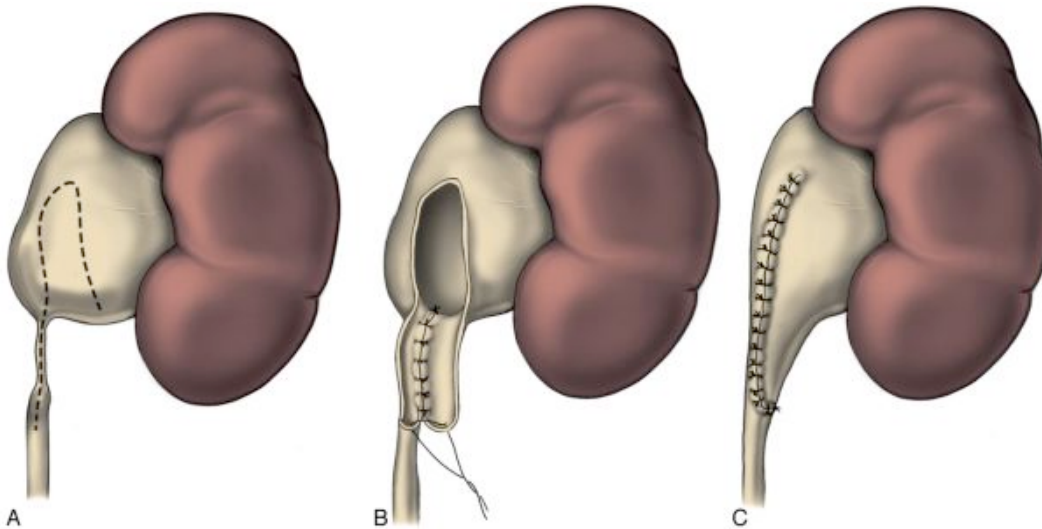
- crossing vessel
- small intra-renal pelvis



→ CULP-DEWEERD SPIRAL FLAP

When would a Scardino-Prince Vertical Flap be preferred?

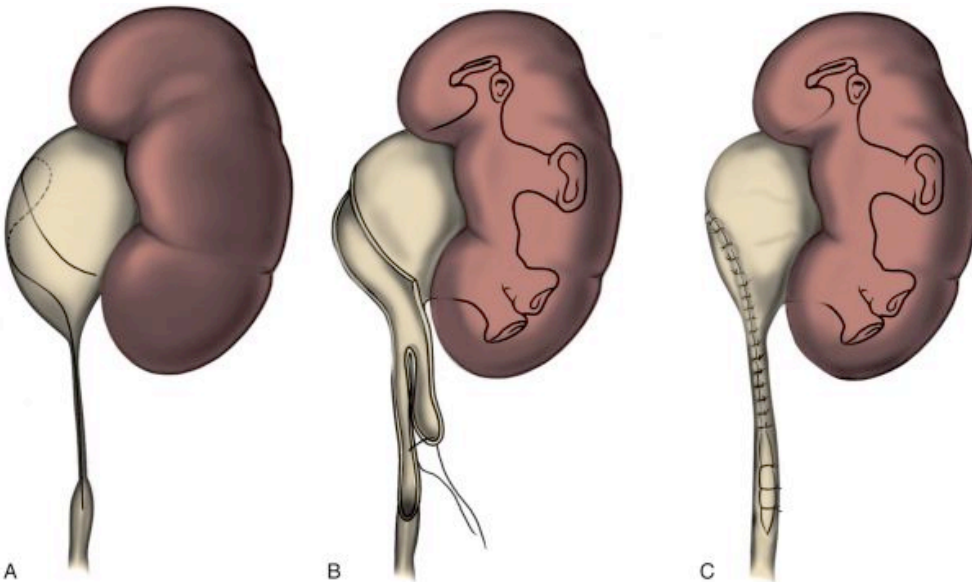
- limited clinical application } now generally replaced by dismembered pyeloplasty
- only good if ureter inserts in a dependent position at the medial margin of a large, square “box-shaped” extrarenal pelvis
- **may be preferred for long areas of proximal ureteral narrowing**
→ CAN’T make flap as long as w/ spiral flap though



→ VERTICAL FLAP

When would a Davis intubated ureterotomy be preferred?

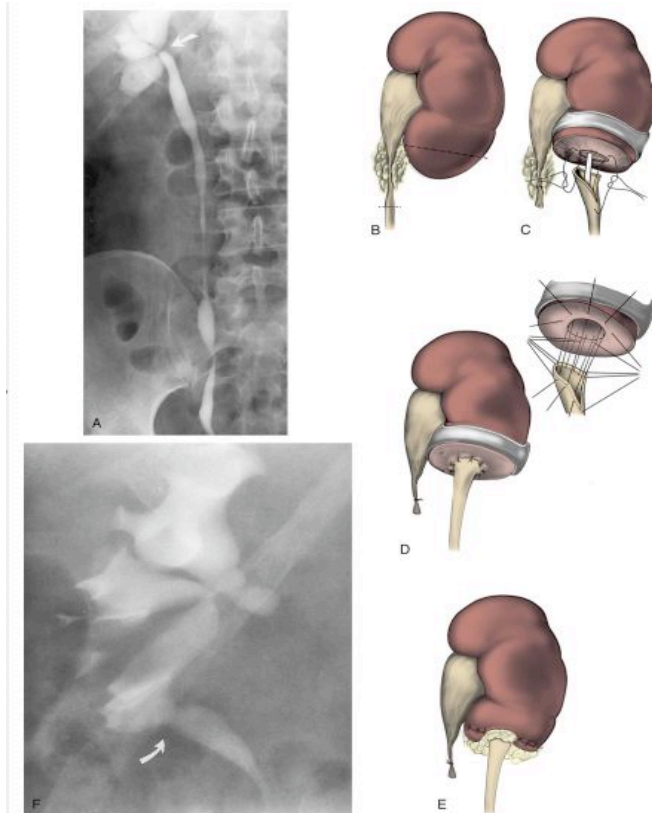
- rarely used today
- **for UPJO associated with multiple or lengthy proximal ureteric narrowing or strictures**
- spiral flap is preferred in this setting



→ INTUBATED URETEROTOMY (distal aspect of ureterotomy left to heal by second intention)

What are the indications for a ureterocalycostomy?

- 1) UPJO with a **small intrarenal pelvis**
- 2) **long proximal ureteric defect**
- 3) associated **rotational anomalies (eg horseshoe)** } provides completely dependent drainage
- 4) **salvage technique for failed dismembered pyeloplasty**



→ URETEROCALYCOSTOMY

Technical Factors

- 1) mobilization of kidney & ureter
- 2) LP heminephrectomy performed (capsule-sparing)
- 3) minimal handling of proximal ureter (preserve vascular supply)
- 4) tension-free, water-tight anastomosis (parachute sutures)
- 5) leave stent & drain
- 6) close renal capsule over cut surface BUT NOT near anastomosis (risk of compression)
- 7) protect anastomosis w/ graft/pedicle of perinephric fat or omentum

What are the options after a failed open pyeloplasty?

- **endopyelotomy procedure → best initial management**
- try flap or dismembered technique not used in first attempt
- ureterocalycostomy
- ileal ureter transposition
- autotransplantation + Boari flap pyelovesicostomy
- nephrectomy

What is the usual post-op care after open pyeloplasty?

- JP removed 24-48 hours later
- stents removed in 4-6 weeks
- antegrade nephrostogram at 7-10 days if NT left in situ
- perc drain if urinoma forms
- imaging 4 weeks after removal of stent/NT

What are the indications for nephrectomy in the setting of UPJ obstruction?

- 1) diminished or non-functioning kidney with N contralateral kidney (<15% differential renal fxn)
- 2) extensive stone disease w/ chronic infection & significant loss of renal fxn w/ N contralateral kidney
- 3) failure of repeated attempts at repair with normal contralateral kidney

Laparoscopic surgery for UPJO

How successful is laparoscopic pyeloplasty?

- in experienced hands, almost as good as open pyeloplasty } ~95% success rate
- better than endopyelotomy
- shorter hospital stay
- lower patient morbidity
- faster convalescence

What are the contraindications to lap pyeloplasty?

- uncorrected coagulopathy
- untreated active UTI
- co-morbidities unsuitable for surgery

What are the different lap pyeloplasty techniques used?

- 1) transperitoneal } most preferred
 - 2) retroperitoneal
 - 3) anterior extraperitoneal
 - 4) robotic-assisted approach
- dismembered Andersen-Hynes pyeloplasty
→ flap pyeloplasty (eg Foley-YV or Culp-DeWeed spiral)

List advantages & disadvantages of retroperitoneal laparoscopic pyeloplasty.

- advantages }
- } lack of adhesions if prior abdo sx
 - } direct access to renal pelvis/hilum
 - } less post-op ileus,
 - } less risk of trocar site hernias
 - } less risk of peritoneal contamination (eg urine, infection, etc)
 - } less post-op shoulder tip pain
- disadvantages }
- } technically challenging (suturing is difficult)
 - } limited working space
 - } less familiar approach
 - } more lung complications (eg pneumothorax)

What is the management of UPJO if lap pyeloplasty is the treatment of choice?

- 1) evaluation
 - History and P/E } r/o contraindications, etc
 - imaging } renal scan, retrograde, etc
 - bloodwork } routine, coag's, etc
 - urine } sterile urine culture pre-op
- 2) lap pyeloplasty
 - +/- pre-op stent placement
 - dismembered pyeloplasty or flap pyeloplasty
 - indigo carmine irrigation into bladder with retrograde flow to assess for anastomotic leak
 - placement of stent
 - Foley and JP drain
- 3) post-op
 - peri-op ABx
 - Foley out in 24-48hrs
 - JP out if dry } reinsert Foley if JP output increases
 - stent in situ for 4-6 weeks
 - f/u renal scan 4-6 weeks after stent removal

What are the complications of laparoscopic pyeloplasty?

- 5-10% complication rate
- colon injury
- renal vessel injury
- hemorrhage
- urinoma formation
- pancreatic injury
- ileus
- pneumonia
- thrombophlebitis

What are the options after a failed lap pyeloplasty?

- endopyelotomy → 1st line } ~70% success rate

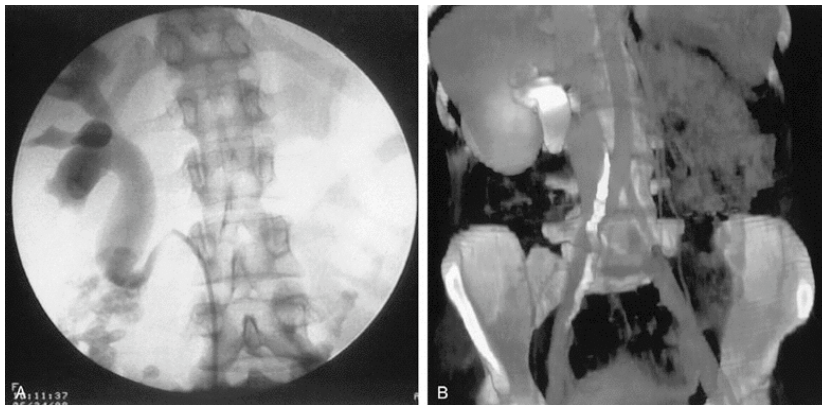
What other laparoscopic surgical techniques are performed for UPJO?

- lap ureterocalicostomy } case report (Gill 2004)
- lap pyeloplasty with concomitant pyelolithotomy } flexible cystoscope via 10-12mm port
- lap dismembered tubularized flap pyeloplasty } case report (Kaouk 2002)
- lap calicovesicostomy } UPJO in pelvic kidney case report (Hsu 2005)

RETROCAVAL URETER

What is a retrocaval ureter?

- rare congenital anomaly
- **actually a congenital abnormality in the development of the IVC not ureter**
 - **failure of SUPRAcardinal vein to develop into infrarenal IVC**
 - **persistence of posterior cardinal/SUBcardinal veins**
- 1 in 1100 and 3x more common in M
- avg age at presentation is 20's and 30's } abdo/flank pain, recurrent UTIs, HTN
- **not always associated with ureteral obstruction**
- usually on R side
- **type 1 (S-shaped fish hook ureter) and type 2 (sickle-shaped ureter)**
 - type 1 usually associated with greater degree of hydro
 - type 2 usually crosses at UPJ and so can be confused with UPJO



→ RETROCAVAL URETER

What are the management options for a retrocaval ureter?

- intervention only if functionally significant obstruction leading to pain or renal function deterioration
- 1) open surgery } pyelopyelostomy – renal pelvis transected and ureter transposed to normal anatomic position anterior to IVC
- 2) lap surgery } transperitoneal or retroperitoneal approach
 - } similar success rates with minimal morbidity

What are the common causes of ureteral strictures (CHART)?

→ acquired

- ## What is the workup for suspected ureteric stricture?

- What are the indications to treat a ureteral stricture?

- ### What are the endourologic management options for ureteral strictures?

1) stent → for acute decompression

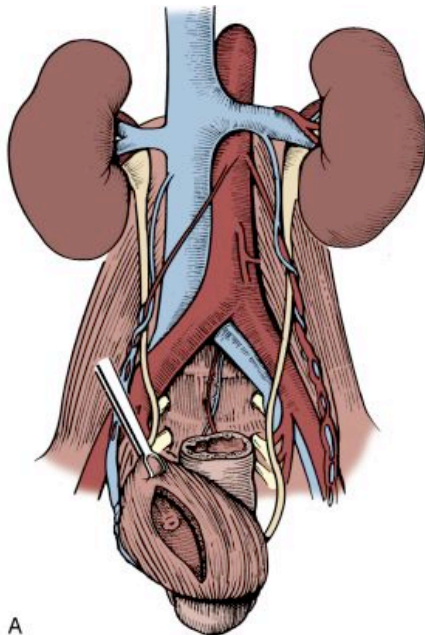
→ not good chronic option for extrinsic causes

- ### What are the open surgical management options for ureteral strictures?

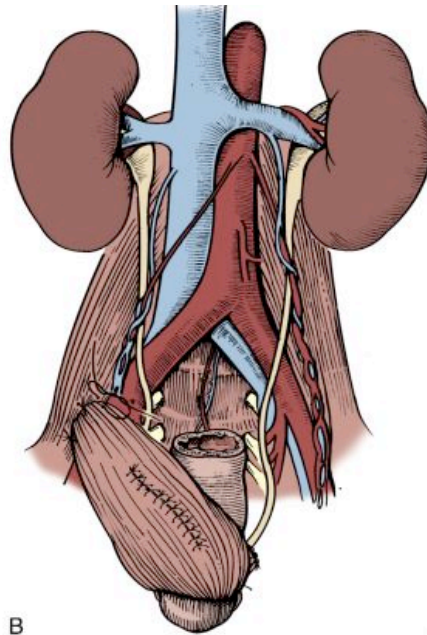
- UU
- reimplant } +/- Psoas Hitch
- } +/- Boari flap
- TUU
- ileal ureter
- auto-Tx

What are the surgical management options for ureteral strictures?

- 1) UU → good for **short upper ureteric or mid-ureteric** strictures
 - flank incision for upper ureter and lower midline or Gibson for mid ureter
 - extraperitoneal dissection unless transperitoneal surgical injury
 - case reports of lap UU
 - dissect and mobilize enough ureter to make tension-free anastomosis
 - with gunshot injury, excise wider to account for blast effect
 - >90% success rate
- 2) reimplant → good for **distal ureteric strictures (3-4cm)**
 - can be combined with Boari flap or Psoas hitch to add length
 - lower midline, Gibson, or Pfannenstiel incision
 - extraperitoneal approach preferred
 - case reports of lap ureteroneocystostomy
 - direct, nontunneled anastomosis or submucosal tunneled anti-reflux anastomosis
 - in adults, no difference in preservation of renal fxn or risk of stenosis (Stefanovic et al 1991)
 - risk of pyelo unclear
- 3) Psoas Hitch → good for **defect in distal 1/3 of ureter (up to level of pelvic brim)**
 - adds 6-10cm of length relative to simple reimplant
 - **CONTRAINDICATED if small, contracted bladder w/ limited mobility**
 - need to evaluate bladder pre-op } treat BOO & neurogenic bladder first
 - lower midline or Pfannenstiel incision
 - extraperitoneal approach preferred
 - case reports of lap Psoas Hitch
 - free peritoneal attachments and divide vas deferens/round ligament
 - for more mobility, **divide contralateral superior vesical artery**
 - ipsilateral bladder dome secured to Psoas tendon/muscle
 - watch for **genitofemoral nerve & femoral nerve**
 - ureter inserted in anterosuperolateral position of bladder
 - >85% success rate

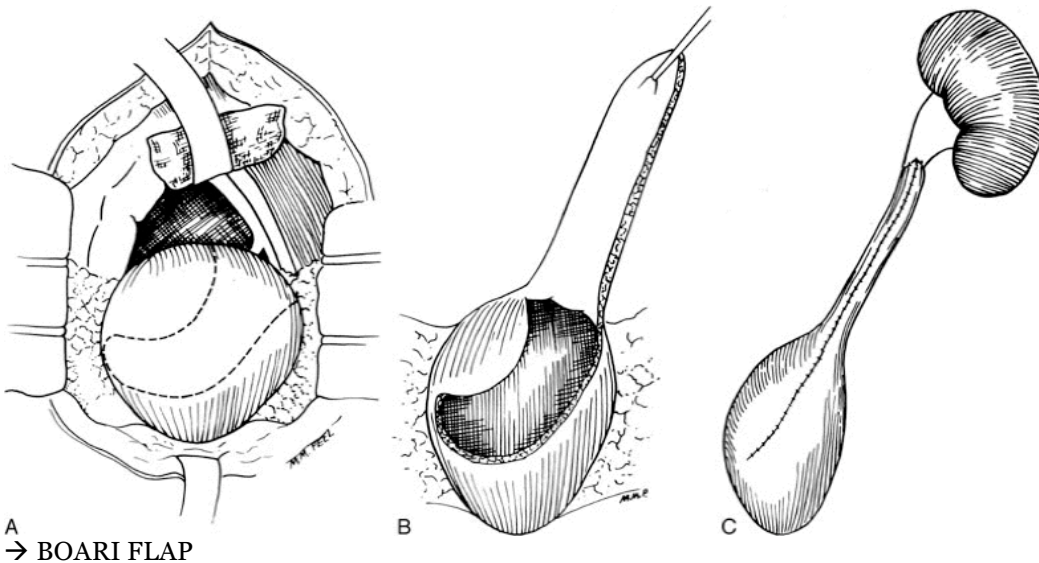


A
→ PSOAS HITCH



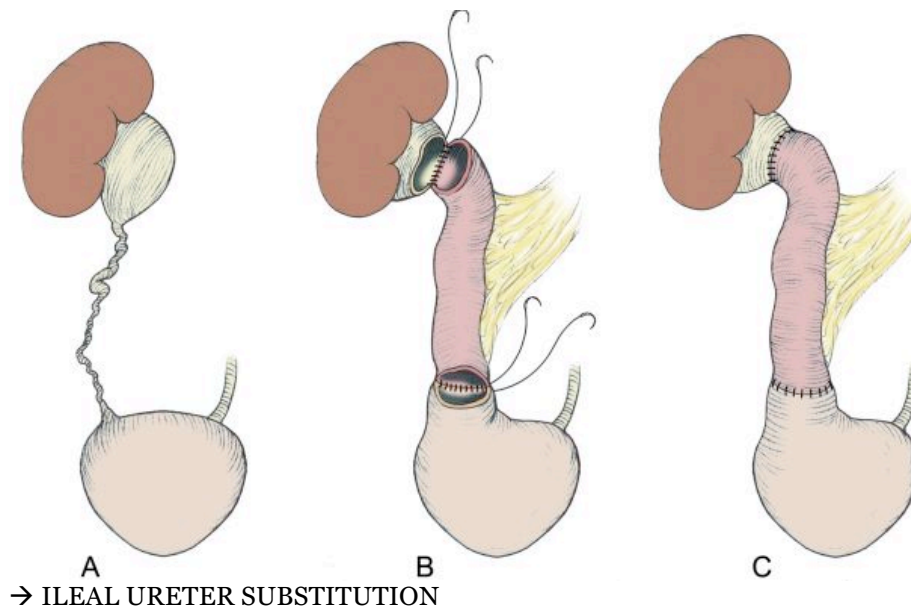
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- 4) Boari flap → good for **distal, mid & some proximal ureteric defects**
- able to bridge 12-15cm ureteral defect
 - spiral flap can reach renal pelvis sometimes, esp on R side
- **CONTRAINDICATED if small, contracted bladder w/ limited mobility**
- need to evaluate bladder pre-op } treat BOO & neurogenic bladder first
- midline incision preferred
- free peritoneal attachments, divide umbilical ligaments, **ligate contralateral bladder pedicle**
- posterolateral bladder flap made based on **vascular supply of ipsilateral superior vesicle artery**
- continue flap to anterior bladder wall
 - base should be at least 4cm, and tip at least 3cm
 - flap length should be enough to cover defect (**3:1** length:width ratio)
- recurrent strictures form due to ischemia or excessive tension



- 5) TUU → good for **mid to lower ureteric defects + length insufficient to reach bladder**
- **ABSOLUTE CONTRAINDICATIONS** include donor ureter too short to reach contralateral side & diseased recipient ureter
- **RELATIVE CONTRAINDICATIONS** include stone disease, RPF, urothelial Ca, chronic pyelo, abdomino-pelvic radiation } VUR can be corrected at time of TUU
- midline incision
- transperitoneal approach
- mobilize colon medially on both sides, expose recipient ureter ~5cm proximal to level of divided ureter, tunnel **under sigmoid colon mesentery proximal to IMA**, anteromedial ureterotomy made, stent placed from kidney of donor side into bladder across anastomosis
- minimize recipient ureter dissection to maintain maximal vascular supply
- 6) intubated ureterotomy → historical procedure no longer used
- 7) renal descensus → good for **upper ureteric defects & to reduce tension on ureteral repairs**
- able to gain 8cm of length } renal vein usually limits descensus
- subcostal, midline, paramedian incision
- transperitoneal or retroperitoneal approach
- kidney mobilized completely and rotated inferiorly and medially
- LP of kidney secured to retroperitoneal muscle

- 8) ileal ureteral substitution → good for **ureteral defects too long for other methods + bladder not suitable for reconstruction**
- **CONTRAINDICATIONS include renal insufficiency, bladder dysfunction or BOO, radiation enteritis, IBD**
 - midline incision + transperitoneal approach
 - mobilize ipsilateral colon medially, measure appropriate length of ileum (15cm from ileocecal valve), divide ileal segment, deliver segment laterally through window in colonic mesentery, ensure isoperistalsis with ureter & anastomose
 - if scarred or intrarenal pelvis, can do ileocalycostomy
 - bilateral ileal substitution can be achieved by long ileal segment that travels intraperitoneally from one kidney to the other, then to the bladder
 - electrolyte abnormalities not common if normal renal function
 - **hyperchloremic metabolic acidosis possible**
 - ureteroscopy of ileal segment recommended starting 3yrs post-op to survey for **malignancy**
 - **Yang-Monti** procedure also option } less small bowel used



- 9) auto-Tx → for **extensive ureteric defects +/- absent/poorly fxn'ing contralateral kidney**
 → can perform nephrectomy laparoscopically
- 10) Nephrectomy

What are the principles of ureteric anastomosis?

- excise devitalized tissue
- limit handling of ureteric tissue
- preserve adventitia to maximize ureteral blood supply
- spatulate widely } if dilated, may transect obliquely to match caliber of lumen
- watertight, tension-free anastomosis
- stent ureter
- if possible cover with retroperitoneal fat or omentum
- place surgical drain (JP)

What ureteral distances are bridged by the different reconstructive techniques?

Procedure	Length of Ureteral Defect (cm)
Ureteroureterostomy	2-3
Ureteroneocystostomy alone	4-5
Ureteroneocystostomy with psoas hitch	6-10
Ureteroneocystostomy with Boari flap	12-15
Renal descensus	5-8

What are the options for a LONG PROXIMAL ureteric stricture/defect?

- 1) Culp-DeWeerd Spiral Flap pyeloplasty
- 2) Scardino-Prince Vertical pyeloplasty
- 3) Davis intubated ureterotomy
- 4) ureterocalycostomy
- 5) Boari flap + Psoas Hitch
- 6) ileal interposition
- 7) renal descensus + UU
- 8) renal auto-Tx
- 9) chronic stent changes
- 10) Nx

URETEROENTERIC ANASTOMOTIC STRICTURE

What factors influence the formation of ureteroenteric anastomotic strictures?

- technique for ureteral dissection
- side (L worse)
- segment of bowel used for diversion
- type of anastomosis

How common are ureteroenteric strictures in ileal conduits?

- 4 to 8%
- more common on L } longer ureteral dissection to cross over to right
- } possible angulation around IMA as L ureter crosses through sigmoid mesentery

How common are ureteroenteric strictures after continent diversion?

- **more common than with IC** } 4 to 25%
- most present within first 2 yrs

Are non-refluxing ureteroenteric anastomoses better or worse?

- higher stricture rate } >5-fold higher
- no clear advantage wrt renal function, colonization, hydro, stones

What investigations are used to assess for ureteroenteric anastomotic strictures?

- U/S } good 1st line
- IVP } good only if sufficient renal function
- CT urogram } can assess for stones, recurrent malignancy, and characterize stricture
- loopogram } helps characterize stricture
- lasix renal scan } to confirm functional obstruction and assess differential function
- antegrade nephrostogram } helps plan management

What are the indications to treat a ureteroenteric anastomotic stricture?

→ most patients with a long-term conduit will have an element of chronic hydro that is NOT due to obstruction

- 1) decline in renal function
- 2) pain
- 3) infections
- 4) stones
- 5) to r/o suspicion of recurrent malignancy

What are the management options for ureteroenteric anastomotic strictures?

- 1) endourologic surgery
 - **1st line therapy (maybe not for L side)**
 - balloon dilation } not good for long strictures
 - } poor overall long-term success rates → 5-15% 3yr success rate
 - electroincision endoureterotomy \
 - cautery wire balloon incision } ~50% long-term patency
 - laser endoureterotomy /
 - Hobbs rather than ureteric stent preferred } mucous plugging
 - **antegrade approach favoured for ureteroenteric strictures**
 - consider open approach for L-sided strictures
 - risk of hemorrhage from surrounding sigmoid mesentery
 - lower overall success rates on the L
- 2) open surgery
 - 2nd line therapy
 - if not enough ureteral length available, may require additional segment of bowel to interpose between ureter and reservoir
 - success rates ~75% at 3yrs
 - lower success rates on the L
 - strictures >1cm more likely to recur

RETROPERITONEAL FIBROSIS

What is RPF?

- condition in which a predominantly inflammatory mass in the retroperitoneum envelops and potentially obstructs retroperitoneal structures } usually at ~L4/L5 level
- 1 in 200,000 with 3:1 male predominance } 15% present with systemic fibrosis
- mean age of onset is 50yrs
- aka Ormond's disease, periureteritis fibrosa, fibrous retroperitonitis
- gross appearance } fibrous, whitish plaque encasing aorta, IVC, and their major branches, ureters, and other retroperitoneal structures; may also involve intraperitoneal structures including the GI tract
- 70% are idiopathic while ~10% are associated with underlying malignancy
- occurs in 2 phases:
 - **inflammatory phase** } plasma cells, lymphocytes, macrophages, and eosinophils
 - inflammation more intense at margins of mass
 - } likely an autoimmune response (?leakage of ceroid lipoprotein from atheromatous plaque in aorta)
 - **fibrotic maturation phase** } development of homogeneous fibrous tissue w/ limited cellularity

What is multifocal fibrosclerosis syndrome?

- syndrome characterized by fibrosis involving multiple organ systems
- RPF
- sclerosing mediastinitis
- sclerosing cholangitis
- orbital pseudotumour
- Riedel's thyroiditis

What other diseases are associated with RPF? } } } "G JAWS"

- immune issue
- **G**lomerulonephritis (membranous)
- **J**RA (kids)
- **A**nkylating spondylitis
- **W**egener's granulomatosis
- **S**LE (kids)

How does RPF usually present?

- 1) history and physical
 - usually presents with non-specific signs and symptoms
 - **back, abdo, flank pain ("girdle-like")**
 - may also have:
 - wt loss
 - anorexia
 - N/V
 - malaise
 - fever
 - HTN (50%)
 - oliguria/anuria
 - lower limb edema
 - DVT
- 2) lab work
 - **elevated ESR (90% - most common)**
 - anemia
 - high creatinine
 - hyergammaglobulinemia

What are the IVP or U/S findings of RPF?

- **hydronephrosis (98%)** } extrinsic compression + interference of peristalsis
- classic IVP triad } medially deviated ureters (nonspecific) + extrinsic ureteric compression
+ proximal hydroureteronephrosis
- smooth, hypoechoic mass anterior to lumbar or sacral spine

What are the usual CT/MRI findings of RPF?

- modality of choice
- no evidence of primary malignancies + no significant lymphadenopathy
- fibrotic plaque has similar HU as muscle
- contrast enhancement of mass common (esp. in areas of active inflammatory fibrosis)
- symmetric, continuous encasement of aorta and IVC
- can't distinguish from great vessels on non-contrast CT
- hypointense compared to muscle on T1 MRI } better discrimination of soft tissue
 - } can distinguish from great vessels
 - } variable GAD enhancement
- more enhancement in acute phase

What are the causes of RPF?

→ **etiology identified in only 30% of cases** } malignancy represents 10% of these cases

Drugs

Methysergide
Hydralazine
Reserpine
Haloperidol
LSD
Methyldopa
 β Blockers
Ergotamine alkaloids
Phenacetin
Amphetamines

Periarteritis

Aortic or iliac artery aneurysm
Inflammatory response to advanced atherosclerosis
Collagen vascular disease

Infection

Gonorrhea
Tuberculosis
Chronic UTI
Syphilis

Chemicals

Avitene
Methyl methacrylate
Talcum powder

Radiation Injury

Other

Sarcoidosis
Biliary tract disease
Endometriosis

Retroperitoneal Tumors

Inflammatory Processes

Ascending lymphangitis
Chronic inflammatory bowel disease

Hemorrhage

Abdominal and pelvic surgery
Ruptured viscera
Henoch-Schönlein purpura with hemorrhage

→ “**RP TIMBIITS**” } } } **Radiation**
Periarteritis (eg AAA)
Trauma (surgical or external)
Infection (eg gonorrhea, TB, syphilis, UTIs, etc)
Meds
Biliary disease
Iatrogenic
Inflammatory (eg IBD)
Tumours (eg lymphoma)
Sarcoidosis

List medications that can cause RPF? } } } “PBL HHAMMER”

- | | |
|--------------------------------------|-----------------------|
| - Phenacetin | - Hydralazine |
| - β-blockers | - Haldol |
| - LSD | - Amphetamines |
| | - Methysergide |
| | - Methyldopa |
| | - Ergots |
| | - Reserpine |

What is the management of RPF?

1) ACUTE MANAGEMENT

- preservation of renal fxn } prompt decompression with NT or JJ stent
 - usually JJ stent goes easily
- } monitor for post-obstructive diuresis
- r/o DVT if lower limb edema
- r/o malignancies
- stop any possible offending meds } spontaneous resolution rare but reported

2) MEDICAL MANAGEMENT } } } "STAMP-C"

- Steroids } r/o malignancy prior to initiating Rx
 - } prednisolone 20-60mg po OD q2days x 6-8wks, then tapered down to 5mg PO OD
 - regression seen up to ~2yrs
 - consider H2 blockers and Ca supplements to decrease S/E's of high dose steroids
- } patients with systemic manifestations or lab evidence of active inflammation tend to respond better
- Tamoxifen } anti-estrogen effects on fibrous tissue (?exact mechanism of action)
 - } 20mg PO OD x 12 months (monotherapy)
 - can also be taken after steroid Rx
 - mainly used after failure of trial of steroids
- immunosuppressants } used in combo w/ steroids or as monotherapy
 - } AZT (2.5mg/kg PO OD x 3-6mos, then 1.5mg/kg PO OD x 6mos)
 - } Cyclophosphamide (2mg/kg PO OD x 3mos, then taper off by 6mos)
 - } Penicillamine and MMF have also been used

3) SURGICAL MANAGEMENT

- 2nd line therapy, after trial of medical management
- always consider treatment of both ureters, even if disease involves 1 ureter
- open Bx +/- ureterolysis } deep Bx sent for frozen and permanent sections
 - } start dissection at distal non-dilated ureter
 - avoid injury to thin dilated proximal segment (strictures and urine leak/fistulae)
 - } mobilize ureter off mass, then reposition + protect ureters
 - retract laterally + secure peritoneum medially
 - displace anteriorly into peritoneal cavity and close peritoneum behind
 - wrap in omentum or PTFE
 - } consider post-op steroids to decrease recurrence
- Laparoscopic Bx +/- ureterolysis } less morbid operation
 - } can be a tough dissection (~15% conversion rate)
- other procedures } excision + reanastomosis, Boari flap, ileal ureter, auto-Tx, Nx

→ long term f/u after medical or surgical therapy is essential

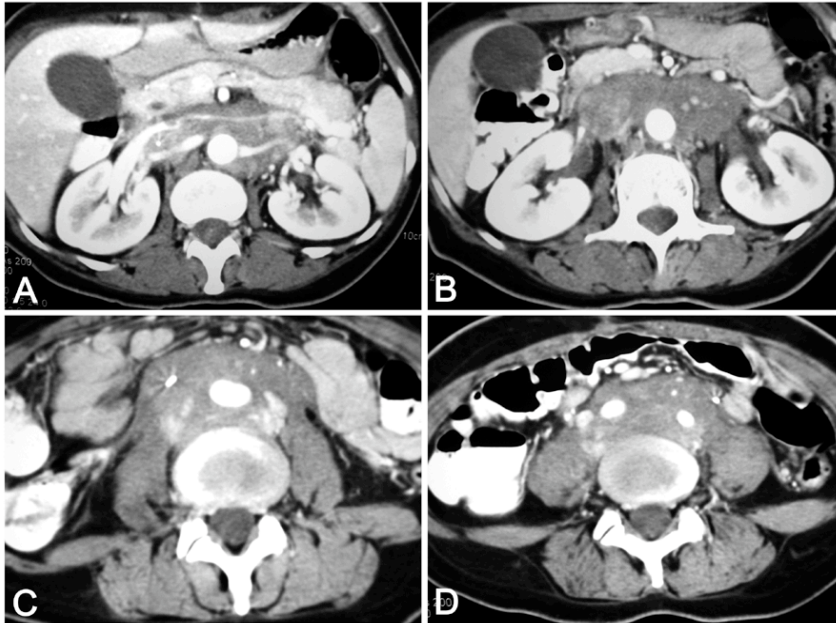
- 1) renal fxn
- 2) findings suggestive of malignancy
- 3) recurrence or progression

List optimal management for AAA associated with RPF. **(AUA UPDATE #3 - 2005)**

- 1) AAA repair + ureterolysis } normalized renal function in 75%
- 2) endovascular repair (EVAR) alone } can resolve RPF in most patients

What are the potential complications of ureterolysis for RPF? **(AUA UPDATE #3 - 2005)**

- **ureteric injury (most common)**
- urine leak
- ureteral strictures
- bowel obstruction } more common if omental wrap performed
- bowel injury
- bleeding
- infection



→ CT SCAN OF RPF

AUA Update #12 - 2008

List the indications for ureteral stent placement.

- obstruction
 - associated with pyelo
 - associated with renal failure
 - solitary kidney
 - bilateral ureteral obstruction
 - refractory renal colic from obstruction stone
 - palliation of renal colic during pregnancy
- promotion of ureteral healing
 - minor perforation
 - major transection, avulsion (repair + stent)
 - persistent urinary extravasation after renal trauma
 - post-op } UPJO repair, ureteral stricture repair, ureteroenteric anastomosis, ureteric reimplantation
 - renal Tx
- prophylactic measure
 - prior to SWL ("SORRI, Stent Patient Before" → eg Solitary, Obstruction, Renal colic, etc)
 - pre-URS to allow passive dilatation (eg paedts)
 - post-complicated URS } not necessary for routine, uncomplicated URS
 - pre-op to assist with intra-op identification of ureter (eg gyne surgery)
- upper tract access
 - upper tract BCG (stent + bladder instillation)

What are the potential complications associated with ureteral stents?

→ intraop

- ureteral injury
- stent migration (usually due to inadequate length)

→ early post-op

- hematuria
- stent colic
- storage LUTs
- stent migration

\ /
stent-related symptoms are the most
common complications

→ late post-op

- UTI
- stent encrustation (most important predictor is indwelling time)
- stent fragmentation
- forgotten stent

What are the physical properties of an ideal stent?

- high tensile strength
- low coefficient of friction
- high degree of radiopacity
- durometer
- high elasticity
- biocompatible
- biodurable

What are the clinical properties of an ideal stent?

- easy to insert
- easy to restore & maintain antegrade flow
- resists migration
- minimal stent symptoms
- cost-effective
- radiopaque
- resist encrustation & biofilm
- biocompatible & biodurable

Chapter #35 – Renal and Ureteral Trauma

RENAL INJURIES

How common is GU trauma?

- 10% of injuries } renal trauma is the most common (2/3 of all GU trauma)

How do renal injuries present?

- 1) history
 - blunt injuries } rapid deceleration or high-velocity-impact trauma
 - penetrating injuries } GSW or stab wound to upper abdomen, flank, or lower chest
- 2) P/E
 - hematuria } **degree of hematuria does not correlate with severity of injury**
 - } can present with microscopic or gross
 - use 1st aliquot of catheterized specimen or initial voided specimen
 - >5RBCs/HPF is considered significant

Why is the kidney prone to trauma?

- mobile organ } puts renal vasculature at risk of injury, especially with rapid deceleration trauma
- located under ribs } rib # can injure kidneys
- intima of artery low in elastic fibers, so disrupts easily

What are the indications for imaging to assess renal trauma?

→ based on study at San Fran General Hospital

- 1) blunt trauma } gross hematuria
 - } microscopic hematuria + shock (sBP <90)
 - } no hematuria but highly suspicious mechanism of injury (eg rapid deceleration)
- 2) penetrating trauma } any degree of hematuria
- 3) kids w/ any degree of hematuria } if <50 RBC/hpf, may not be needed?? (AUA Update)

What imaging studies are required to stage renal trauma?

- CT with contrast and delayed images (~10mins)
 - limitation is inability to define renal venous injury adequately
- IVP (intra-op, single-shot film)
- arteriography } limited role initially

What findings on CT suggest major renal injury?

- medial hematoma (vascular injury or UPJ injury)
- medial urinary extravasation
- lack of contrast enhancement of parenchyma (arterial injury)

What are the CT findings suggestive of renal vascular injury?

- medial hematoma
- lack of enhancement of parenchyma
- kidney displaced laterally

What are the indications for an intra-op, single-shot IVP?

- unexpected retroperitoneal hematoma
- incomplete staging (unstable for imaging) + suspicion for renal injury
 - exploration indicated if study is abN or near normal

How do you perform an intra-op, single-shot IVP?

- iv push of 2 mL/kg of contrast material
- film taken at 10min post-injection

What is the DDX of non-visualization of one kidney during IVP?

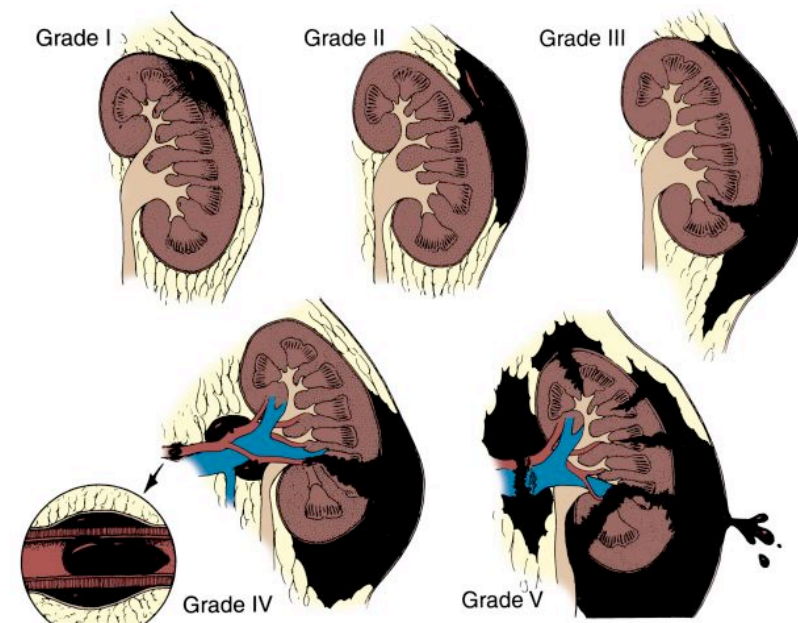
- absence of kidney } congenital agenesis
- } ectopic kidney
- } Nx
- decreased perfusion } systemic hypoTN
- } unilateral renal vein thrombosis
- } renal artery occlusion/thrombosis
- } pedicle avulsion (trauma)
- high-grade obstruction } chronic obstructive uropathy
- replaced normal renal parenchyma } MCDK
- } renal tumour
- } XGP
- } chronic pyelonephritis

What are the indications for arteriography?

- to define arterial injury suspected on CT
- to localize arterial bleeding that can be controlled by embolization
- to assess and treat delayed AVF that develops

What is the AAST classification of renal injuries (CHART)?

- grade 1 } renal contusion (hematuria + N imaging)
 - OR subcapsular hematoma (nonexpanding)
 - grade 2 } nonexpanding perirenal hematoma (confined to retroperitoneum)
 - OR laceration (<1cm)
 - grade 3 } laceration >1cm WITHOUT violation of collecting system or urinary extravasation
 - grade 4 } laceration into collecting system
 - OR main renal artery or vein injury w/ contained hemorrhage (including segmentals)
 - grade 5 } shattered kidney
 - OR avulsion of renal hilum (devascularized kidney)
- *** advance one grade for bilateral injuries, up to grade 3 ***



→ RENAL TRAUMA CLASSIFICATION

Management

What is the non-operative management of renal injuries?

- ~95% of renal injuries are grade 1
- 98% of blunt renal injuries can be managed non-operatively
- ~50% of stab wounds and ~25% of GSW can be managed non-operatively
- 80% of renal injuries have major associated organ injury
- 1) ABC's
- 2) admission and close monitoring of VS's
- 3) bedrest until gross hematuria resolves; reinstate bedrest if gross hematuria returns w/ ambulation
- 4) Abx if urinary extravasation
- 5) serial HgB and prn imaging
- 6) embolization for persistent bleeding or delayed bleeding } take to OR if not successful
- 7) repeat imaging for grade 3-4 injuries (U/S likely ok .. AUA update 2006)
- 8) ureteric stent or perc drain if continued urinary extravasation >48hrs
- 9) no strenuous activity for 6 weeks

What are the indications for renal exploration in renal trauma?

- ~85% of grade 4 renal injuries w/ urinary extravasation alone resolve with non-operative mgt
- 1) ABSOLUTE
 - expanding perirenal hematoma \ one-shot IVP to confirm
 - pulsatile perirenal hematoma / presence of other kidney
 - vascular injury in solitary kidney (or bilateral vascular injury)
 - unstable patient with evidence of persistent renal bleeding
- 2) RELATIVE
 - urinary extravasation
 - nonviable tissue with urinary extravasation
 - high complication rate if >20% nonviable tissue + laceration + urinoma
 - delayed Dx of arterial injury
 - segmental arterial injury
 - incomplete staging

What is the approach to surgical exploration for renal trauma?

- transabdominal approach best } can assess other organs
- isolate renal vessels } RP incision made over aorta just superior to IMA & medial to IMV
 - } early vessel isolation decreases Nx rate from ~50% to 20%
 - } some have shown Nx rate, without early isolation, to be only ~35%
- mobilize colon off Gerota's fascia
- open Gerota's and dissect kidney free of surrounding hematoma

What are the principles of renal reconstruction after trauma?

- complete renal exposure
- debridement of nonviable tissue
- hemostasis with individual suture ligation of bleeding vessels
- watertight closure of collecting system
- coverage or approximation of parenchymal defect

What types of renal vascular injuries are common in trauma?

- **associated with multiple non-renal organ injuries and a high mortality rate (20-45%)**
- arterial } stretch from blunt deceleration causes intimal tear and formation of thrombus
 - } results in **renal artery thrombosis** and ischemia
 - **surgical revascularization seldom successful**
 - if arterial thrombosis Dx'd, need to operate **within 8hrs** to save kidney
 - "cortical rim" sign likely means delayed presentation of arterial injury
 - **main renal artery injuries usually require intervention** (Nx or vascular repair)
 - Nx preferred } no benefit to vascular repair, especially in blunt trauma
 - endovascular revascularization may have a role } anticoagulation is often an issue
 - **segmental artery injuries are usually observed** unless associated with parenchymal laceration or >20% non-viable tissue
- venous } usually a venous tear requires closure with 5-0 prolene
 - **if small laceration or thrombosis, can try conservative non-operative mgt**
 - segmental venous injuries best managed by ligation (collateral venous drainage)

What are the indications for Nx after renal trauma?

- sometimes patient is too unstable to attempt renal reconstruction
- damage control (packing off area) is an option
- 1) extensive renal injury threatening life
- 2) extensive renal injury with non-salvageable kidney

What are the potential complications following renal trauma?

- urinoma
- perinephric infection
- perinephric abscess (rare)
- renal loss
- delayed renal bleeding } usually occurs within 21 days
- HTN (late) } should resolve within 6 wks
- AVF (late)

How does HTN occur post-renal trauma?

- activation of RAAS by partial renal ischemia
- 1) renal vascular injury, leading to stenosis or occlusion of main/segmental renal artery
- 2) compression of renal parenchyma with extravasated blood or urine (Page kidney)
- 3) post-trauma AVF

URETERAL INJURIES

How common is ureteric trauma?

- rare after external trauma } <4% of penetrating trauma and <1% of blunt trauma
- when related to GSW, significant assoc'd injuries are often present (mortality rate of ~33%)
- less common w/ blunt injuries, unless extreme force } lumbar process #, thoracolumbar spinal dislocation
- 10-30% have associated renal injuries
- 5% have associated bladder injuries

What is the classification of ureteral trauma (NEW)?

- grade 1 } contusion or hematoma without devascularization
- grade 2 } <50% transection
- grade 3 } ≥50% transection
- grade 4 } complete transection with <2cm devascularization
- grade 5 } avulsion with >2cm devascularization
- *** if bilateral, advance one grade up to grade 3 ***

What are the imaging studies used to stage ureteral injuries?

- **CT with contrast and delayed films } need urogram phase to trace ureters to bladder**
- intra-op, "single-shot" IVP } not very sensitive
- retrograde pyelogram } mainly to Dx missed ureteral injuries or further stage ureteral injuries seen on CT/IVP

What are the findings on CT suggestive of a UPJ disruption?

- difficult Dx because pt may not have hematuria and the injury is difficult to palpate during intra-op examination } **in kids, should do laparotomy and fix open**
- 1) medial contrast extravasation
- 2) circumrenal contrast extravasation
- 3) non-opacification of ipsilateral ureter

What are the most common iatrogenic causes of ureteral trauma?

- hysterectomy (54%) \ usually are symptomatic early in the post-op period and often
- colorectal surgery (15%) / require reconstructive surgery or Nx
- pelvic surgery (eg ovarian tumour removal and transabdominal urethropepy)
- lap gyne surgery (eg lysis of endometriosis) } fewer injuries are recognized intra-op cf open surgery
- abdominal vascular surgery } often may get hydronephrosis but the course is benign in most and occurs only in 1-2%
- urologic surgery (eg ureteroscopy)

What are the RFs for intra-op ureteral injury?

- previous pelvic Sx
- operating at pelvic brim (most common site of ureteral injury during gyne OR)
- distorted anatomy at pelvic sidewall
- removal of adnexa after previous TAH
- removal of ovarian processes including endometriosis, Ca, etc
- repair of bladder injuries
- AAA repair

What are the RFs for ureteric injury during abdominal vascular surgery?

- 1) re-operation
 - 2) placement of a vascular graft anterior to the ureter
 - 3) large dilated arterial aneurysm that causes retroperitoneal inflammation
- most ureteric injuries after vascular surgery are NOT recognized immediately
 - present with flank pain (35-90%), fever, ileus, abdominal distension, urinary fistula, etc

What is the role for pre-op stenting to prevent iatrogenic ureteric injuries?

- **likely increases intra-op recognition but does not decrease ureteric injuries**
- placement of stent can have complications } injury, failed placement, etc
- some recommend iv indigo carmine + cysto after lap gyne surgery to assess ureters

What are the RFs for ureteric injury during ureteroscopy?

- long OR time
- treatment of renal stones } some energy modalities are higher risk than others (eg EHL)
- surgeon inexperience
- previous radiation
- use of rigid ureteroscopes

How do ureteric injuries present?

- 25-45% do not have even microscopic hematuria
- must have high index of suspicion based on mechanism and location of injury
- most patients with ureteric injury have significant associated injury and so often undergo laparotomy
- ureteric injuries are often Dx'd intra-operatively
- also often have a delayed presentation } bullet has ischemic effect on surrounding tissue that results in delayed injury

What are some of the delayed signs of ureteric injury?

- often present >48hrs after injury
- fever
- WBC
- hydronephrosis
- hematuria
- local peritoneal irritation
- ileus or N/V
- urine leak/fistula
- anuria

List maternal GU complications after C-section.

- ureteric injury
- bladder injury
- urinoma
- pelvic abscess
- hydronephrosis
- uretero-uterine fistula
- vesico-uterine fistula
- urethral diverticulum \ from prolonged labour
- urethrovaginal fistula / prior to C-section

Management

What is the management of ureteral contusions?

- observation & conservative management
- UU } severe or large areas of contusion often heal w/ stricture or slough later on resulting in necrosis
- } excision of damages area + UU

What are the general principles of ureteric surgery?

- 1) mobilize ureter carefully, preserving adventitia and blood supply
- 2) debride the ureter liberally until bleeding edges (especially important in high-velocity GSW)
- 3) repair ureters in spatulated, tension-free, water-tight fashion
- 4) anastomosis made over stent
- 5) drain retroperitoneum
- 6) consider omental interposition to isolate repair
- 7) use absorbable suture material

What are the potential complications following a UU?

- acute } 10-20%
 - urine leak
 - abscess
 - fistula
- chronic } 5-10%
 - ureteral stenosis (most common chronic complication)
 - persistent fistula
 - renal deterioration

What are the management options for UPPER ureteric injuries?

- 1) UU } if short
- 2) ureterocalycostomy } for profound damage to the renal pelvis and UPJ
- 3) auto-Tx } for profound ureter loss or after multiple failed attempts at repair
 } 5-10% rate of loss of renal unit after auto-Tx
- 4) bowel interposition } when long segments of ureter destroyed
 } ileal ureter, appendix, Yang-Monti
 → NOT good option for acute repair
 } avoid if renal insufficiency
- 5) chronic stent or NT changes
- 6) Nx
- ?7) Flap procedures (eg Culp-DeWeerd, Scardino-Prince, etc)

What are the options for a LONG PROXIMAL ureteric stricture/defect?

- 1) Culp-DeWeerd Spiral Flap pyeloplasty
- 2) Scardino-Prince Vertical pyeloplasty
- 3) Davis intubated ureterotomy
- 4) ureterocalycostomy
- 5) Boari flap + Psoas Hitch
- 6) ileal interposition
- 7) renal descensus + UU
- 8) renal auto-Tx
- 9) chronic stent or NT changes
- 10) Nx

What are the management options for MID ureteric injuries?

- 1) UU +/- renal descensus
- 2) TUU } successful in adults (>90%) more than kids (70%)
 } NOT good option for acute repair
- 3) bowel interposition
- 4) Boari flap } 3:1 length-to-width ratio (minimum 4cm base and 3cm tip of flap)
- 5) ureterocutaneous fistula

What are the contraindications for TUU repair of a ureteral injury?

→ absolute

- ureteric segment too short to reach
- diseased recipient

→ relative

- hx of stones
- hx of pelvic RADs
- hx of GU TB
- hx of urothelial carcinoma
- hx of recurrent pyelonephritis
- contralateral hx of GU surgery
- any anatomic abnormality of contralateral/recipient ureter (eg VUR, RPF, etc)
- any disease process involving both ureters

What are the management options for DISTAL ureteric injuries?

- 1) ureteroneocystostomy (reimplant) } for very distal ureteric injuries
 } Lisch-Gregoire reimplant
- 2) Psoas Hitch } high success rate (>95%)
- 3) Boari flap } when long segment of distal ureter destroyed
 } may not be good option for acute repair

Procedure	Length of Ureteral Defect (cm)
Ureteroureterostomy	2–3
Ureteroneocystostomy alone	4–5
Ureteroneocystostomy with psoas hitch	6–10
Ureteroneocystostomy with Boari flap	12–15
Renal descensus	5–8

What is the management of a partial transection of a ureter?

- primary repair } must be limited to stab wounds and low-velocity GSWs
} convert longitudinal incision into transverse so as not to narrow lumen (Heineke-Mikulicz procedure)

What is the management of ureteric injuries if the patient is too unstable to tolerate the OR time?

- 1) stage repair
 - a) do nothing but plan OR once stable (usually within 24hrs)
 - b) place ureteral stent and do nothing else
 - c) exteriorize the ureter (ureterocutaneous fistula)
 - d) tie off ureter & plan perc NT
- 2) Nx

What are the indications for Nx after ureteral injuries?

- severe associated visceral injuries
- severe ipsilateral renal injury + repair not possible
- poor renal function after delayed Dx
- severe pan-ureteric injury
- persistent ureteral fistula
- ureteral injury during vascular graft placement } relative indication now
} most will try to save kidney
→ repair, stent, omental wrap +/- drain

What are the management options for iatrogenic ureteric injury?

- 1) ligation } removal of ligature and observe ureter for viability
} if viability is questionable, perform UU or reimplant
} place stent by opening bladder or by cystoscopy
- 2) transection
 - immediate recognition } usually treated same as ureteral trauma (upper, mid, distal)
} consider Nx if vascular graft surgery (urine leak around graft can be potentially fatal), although renal dysfunction after aortic aneurysmectomy ranges from 3-12%
 - delayed recognition } stent placement (successful only in 20-50%) x 6wks
} early open repair (may run into more complications)
} NT + delayed repair (>6weeks)
→ open repair vs endourologic repair
→ balloon dilation, laser incision, etc reserved for short strictures only
- 3) ureteroscopic avulsion } usually treated same as ureteral trauma
- 4) ureteroscopic perforation } stent placement (usually no complications)

When is the best time to repair a ureteric injury?

- intraop Dx → immediate repair
- <POD#5-7 at Dx → retrograde + stent preferred
→ immediate repair ok if complex
- if >POD#5-7 at Dx → stent or NT
→ drain urinoma
→ delayed reconstruction

What is the follow-up management of repaired ureteric injuries/trauma?

- stent left in situ at least 6 weeks
- consider retrograde pyelogram at time of stent removal
- lasix renal scan and/or U/S at 4-6 weeks (or earlier if symptoms develop)
- surveillance with lasix renal scan and/or U/S
- if 6 weeks of stenting is unsuccessful consider endoscopic treatment
 - laser incision, balloon dilation, etc
 - if unsuccessful, consider open repair

Chapter #40 – Renal Transplantation

ESRD

How common is ESRD?

- median age is 65yrs } more common in elderly, in men & in Blacks/Hispanics
- DM is most common cause; HTN and GN are 2nd and 3rd most common
- more common than any GU malignancy (except PCa) and has higher mortality than any GU malignancy

What is the definition of permanent ESRD?

- irreversible GFR <10 mL/min (or <15)
- serum creatinine >8 mg/dL (>720 µmol/L)
- symptomatic uremia

What are the stages of chronic kidney disease?

→ National Kidney Foundation 2002

- stage 1 } kidney damage with N or increased GFR (**≥90 mL/min/1.73 m²**)
→ Dx and treat CKD, treat comorbid conditions, slow progression, reduce CVS risk
- stage 2 } kidney damage with mild decrease in GFR (**60–89**)
→ estimate progression
- stage 3 } moderate decrease in GFR (**30–59**)
→ evaluate and treat complications
- stage 4 } severe decrease in GFR (**15–29**)
→ evaluate and treat complications
- stage 5 } kidney failure (**<15 or dialysis**)
→ RRT

What are the causes of CKD/ESRD?

→ most forms of CKD progress to ESRD over a 2 to 10yr time course

- 1) **DM (~50%)**
- 2) **HTN (~25%)**
- 3) **GN (~10%) } much more common cause outside N America**
- 4) interstitial nephritis/pyelonephritis
- 5) unknown
- 6) miscellaneous } sickle cell disease, AIDS, trauma, hepato-renal syndrome, etc
- 7) hereditary/congenital cystic disease
- 8) secondary GN/vasculitis
- 9) cancer/tumour

What are the options for ESRD?

- peritoneal dialysis } ~10%
- hemodialysis } >50%
- renal transplantation

What are the ideal characteristics for PD?

- desire for self-care
- long distance from HD unit
- difficulties with HD
- serious cardiac disease
- small stature
- DM (???) } older DM patients do better on HD

What are the unsuitable characteristics for PD?

- obesity
- hernias
- poor hygiene
- IBD
- obliterated peritoneal space

What are the indications to change to PD?

- recurrent CHF
- access failure
- hypercoagulability
- malnutrition
- poor tolerance of HD (intradialysis hypoTN)
- nursing home care

What are the indications to change to HD?

- recurrent peritonitis
- catheter malfunction
- UF failure
- psychological burnout
- failure of ADLs
- hospitalization
- uncontrolled DM
- hypoTN

What are the advantages of living renal Tx compared to DD renal Tx?

- better graft survival } shorter ischemic time, less DGF
- less recipient morbidity
- specific OR planning to allow pre-emptive Tx or limit time on HD
- partial alleviation of long list of patients waiting for DD renal Tx

What are the complications of ESRD?

- cardiovascular disease } 60% with CRF die of CV disease before dialysis
- HTN
- infections
- neuropathy
- anemia
- malnutrition
- bone disease
- altered QOL

What are the specific problems in kids with ESRD?

- 1) growth failure } can use GH
- 2) poor nutrition } can give feeds via G-tube
- 3) psychiatric problems (depression, loss of self-esteem, etc)

What is the effect of renal Tx on mortality rates?

- survival significantly better after Tx } not just a result of healthier patients undergoing Tx
- **regardless of whether on HD or Tx major causes of death in patients with ESRD are:**
 - 1) heart disease
 - 2) sepsis
 - 3) stroke

How long do renal grafts last (CHART)?

- HLA identical sibling } 87% 5yr survival
- one-haplotype sibling } 81% 5yr survival
- living unrelated donor } 78% 5yr survival
- deceased donor } 66% 5yr survival
 - standard criteria } 70% 5yr survival
 - extended criteria } 52% 5yr survival

SELECTION AND PREPARATION OF KIDNEY TRANSPLANT RECIPIENTS

What is involved in the evaluation of renal Tx candidates?

- 1) preliminary screening
 - substance abuse } random drug screening
 - morbid obesity } weight loss
 - compliance issues } contract
 - high risk for heart disease } assess for CAD, must stop smoking
- 2) evaluation
 - history } medical, surgical, immunization, meds
 - P/E } FOBT, pap smear, dental exam, eye exam (if ≥50yrs or DM), DRE
 - lab work } PPD, CBC, lytes, creatinine, INR, PTT, PSA, infectious serology, U/A, urine C&S
 } histocompatibility testing
 - imaging } CXR, abdo U/S, EKG, mammogram (if ≥40yrs)
 - allied health } SW consult, dietary consult, financial counseling, psych counseling, patient & family education
- 3) special studies and consults PRN
- 4) r/o contraindications

What causes of ESRD commonly recur after renal Tx? } } } “FOH, FAC, DI”

- 1) FSGS } **esp. if <15yo, rapidly progressive course, or if mesangial proliferation on Bx**
 } 50% recurrence after Tx, risk of recurrence ~80% in 2nd Tx if recurrence in 1st Tx
- 2) Oxalosis } need to correct metabolic defect by doing combined liver & kidney Tx
- 3) HUS } recurrence more common if on cyclosporine immunosuppression
- 4) Fabry's disease \
- 5) renal Amyloidosis } recurs but can be manageable
- 6) Cystinosis /
- 7) DM \ **can recur but DOES NOT**
- 8) IgA nephropathy / **cause graft failure**

What causes of ESRD do not recur after renal Tx?

- 1) AD PCKD
- 2) renal dysplasia (genetic, from reflux, etc)
- 3) Alport's syndrome without anti-glomerular BM Ab's

What immunizations are given prior to renal Tx?

- DPTP
- MMR
- Hepatitis A and B
- varicella
- pneumococcus

What is the recommended wait times after invasive malignancies?

- 2-5yrs } breast Ca, Colon Ca, melanoma
- 2yrs } large RCC, Wilms tumour, invasive TCC, testis Ca, PCa, thyroid Ca, lymphoma, SCC of skin
- no wait } small/incidental RCC (perform simultaneous Nx), non-invasive TCC, BCC of skin

What infectious serologic testing is performed prior to renal Tx?

- CMV } if seropositive donor or seropositive recipient, graft survival rates are worse
- HSV
- EBV } **seronegative to seronegative has lower risk of post-Tx lymphoproliferative disorder (PTLD) → most common new malignancy in kids**
- HIV
- HBV and HCV } if active, combination IFN-α + ribavirin

What are the recommendations for Doppler Flow studies prior to renal Tx (CHART)?

- 1) carotid Doppler
 - cerebrovascular symptoms or bruits
- 2) aortoiliac arteries, splenic and renal arteries, and lower extremity arteries
 - lower limb claudication or bruits
 - extensive aortoiliac calcifications or bruits
 - prior B/L renal Tx
 - prior abdominal vascular surgery
 - prior abdominal radiation
- 3) pelvic veins and IVC
 - prior B/L renal Tx
 - prior abdominal vascular surgery
 - prior abdominal radiation
 - prior pelvic DVT

What are the RFs for graft thrombosis after renal Tx?

- previous vascular access graft (AVF) thrombosis
 - previous DVT
 - anti-phospholipid Ab (~40% with SLE)
 - previous large vein renal Tx thrombosis
 - nephrotic syndrome (loss of natural anticoagulants such as anti-thrombin 3, protein C&S)
 - hyperhomocysteinemia
- more common in kids } esp. if child too small and can't perfuse kidney well enough

What are the indications for additional urologic studies prior to renal Tx?

- VCUG +/- UDS } voiding dysfunction, hx of pyelo or reflux, abN U/S
- cysto } suspected lower tract Ca, planned invasive prostate Rx, non-glomerular hematuria
- retrograde pyelography } planned orthotopic renal Tx
- renal CT } AD PCKD, inconclusive U/S for stones or masses
- urine cytology } prior cyclophosphamide or irritative LUTS
- bladder biopsy } suspected fibrosis or cancer
- retrograde loopogram/pouchogram } intestinal conduit, reservoir

How does smoking affect renal Tx outcomes?

- ↑'d risk of complications } → peri-op M&M
 - post-Tx malignancy
 - post-Tx CV disease
 - renal graft loss

How does renal transplantation affect ED?

- **caused by atherosclerosis, psychologic effects, anti-HTN'sive meds, hyperprolactinemia**
- ESRD-associated ED (common) improves significantly after renal Tx
 - if prosthesis required before renal Tx, don't use one with prevesical reservoir

What are the indications for pre-Tx cholecystectomy?

- recurrent biliary colic or previous cholecystitis
- stone w/ GB wall thickening
- polyp >1cm
- multiple small stones

List contraindications to renal Tx. } } } “I PUNT BAC”

- Infection (active)
- Poor surgical candidate } high chance of peri-op M&M (incl. morbid obesity)
- Urologic or vascular conditions technically unsuitable
- Neoplasia (active or recent)
- T cell HLA crossmatch +ve
- Brain injury (irreversible)
- ABO incompatibility
- Compliance issue or substance abuse

What are the indications for pre-Tx nephrectomy (CHART)? } } } “MASHHH PPPP”

- 1) Malignant mass +/- acquired renal cystic disease
- 2) persistent Anti-glomerular BM Ab levels
- 3) Stones not cleared by minimally invasive techniques or SWL
- 4) Hydronephrosis (severe)
- 5) Hematuria (severe)
- 6) HTN (intractable to meds)
- 7) significant Proteinuria not controlled with embolization or medical Nx
- 8) recurrent Pyelo
- 9) PCKD that is symptomatic, extends below iliac crest, gets infected, or has solid tumours
- 10) Polyuria (severe)

What are the different types of cross-matches?

- 1) T cell cross-match
 - recipient serum (Ab's) WITH donor lymphocytes (class I Ag's)
 - takes ~6hrs
 - +ve T cell cross-match results in 80-90% hyperacute rejection } contraindication to Tx
- 2) B cell cross-match
 - recipient serum (Ab's) WITH donor lymphocytes (class II Ag's)
 - +ve B cell cross-match results in only slightly worse outcomes } NOT contraindication to Tx

DONOR SELECTION, PREPARATION, AND SURGERY

What are the basic criteria to be a suitable renal donor?

- 1) absence of renal disease
- 2) absence of active infection
- 3) absence of transmissible malignancy
- 4) mental competence to consent to surgery

What are the surgical goals of renal graft retrieval?

- minimize warm ischemia time
- preserve renal vessels
- preserve ureteral blood supply

What are the contraindications to donor Nx?

- “Robinette WON’T Make Cut”
 - significant Renal disease (or potential for renal disease - DM)
 - Work-up abnormality (eg cardiac, endocrine, infectious, etc)
 - Operative risk (high chance of M&M)
 - Neoplasia
 - Transmissible infection
 - Mental dysfunction
 - Coerced or involving financial transaction
- relative } ABO incompatibility or +ve crossmatch (plasmapheresis, high-risk protocol, etc)
- } significant anatomic abnormality (eg multiple ureters, vessels, etc)

Living Donor

Which kidney is preferred for donation?

- **worst of the two kidneys is donated**
- R kidney preferable in young women } risk of hydronephrosis & pyelo of pregnancy more common on R
- L kidney preferred otherwise } longer renal vein
- **donor urine output just prior to Nx is best predictor of early graft function**

What is involved in the evaluation of a potential renal donor?

- 1) history and physical
 - medical and surgical hx
 - meds, allergies
 - BP + general physical
- 2) initial lab work
 - CBC, lytes, creatinine
 - urinalysis
 - blood sugar
- 3) ABO blood type
- 4) **r/o contraindications** ("Robinette WON'T Make Cut")
 - significant mental dysfunction
 - renal disease
 - high risk for peri-op morbidity or mortality
 - significant transmissible disease
- 5) donor-recipient crossmatch
- 6) complete lab work
 - glucose tolerance test
 - infectious serology (HIV, HTLV-1, CMV, EBV, syphilis, hepA, hepB, hepC)
 - pap smear (women)
 - pregnancy test
 - PSA (blacks if ≥40yrs, other men if ≥50yrs)
- 7) imaging
 - CXR
 - EKG
 - mammogram (if ≥40yrs or family hx of breast Ca)
- 8) assessment by SW and psychiatry
- 9) repeat evaluation
 - current hx and P/E
 - repeat CBC, lytes, creatinine, urinalysis, PT, PTT
 - repeat CXR, EKG
 - FOBT
 - PPD
- 10) GU tract imaging
 - triphasic abdo/pelvis CT
- 11) final crossmatch

What is the long-term sequelae of having a solitary kidney?

- achieve **80% baseline GFR** } sustained long term
- development of HTN same as general population
- development of proteinuria negligible
- donating kidney has been associated with survival benefit
 - selection bias } extensive medical tests

What are the reported advantages & disadvantages of laparoscopic renal donor Nx?

→ advantages

- decreased pain meds
- decreased length of stay
- earlier return to work

→ disadvantages

- increased OR time
- donor surgeon preference for L kidney
- increased cost
- longer warm ischemic times
- delayed graft function
- worse long-term graft survival (debatable)

Deceased Donor

What are the criteria for an ideal deceased donor?

- N renal function
- no HTN
- no DM
- no malignancy other than a primary brain tumour or treated superficial skin Ca
- no generalized viral or bacterial infection
- acceptable urinalysis
- age between 6yrs and 50yrs
- negative assays for syphilis, hepatitis, HIV, HTLV

What is the definition of an “extended criteria donor”?

- 1) age >60yrs
- 2) 51-59yrs of age with any 2 of the following:
 - cerebrovascular death
 - HTN
 - serum creatinine >1.5 mg/dL (>135 µmol/L)

What findings on deceased donor kidney Bx suggest marginal function?

- **glomerulosclerosis } don't accept kidney if >20% glomerulosclerosis**
 - interstitial fibrosis
 - tubular atrophy
 - vascular narrowing
- may consider transplantation of both kidneys from a marginal donor

What are the initial goals of resuscitation of brain-dead deceased donors?

- sBP ≥90mmHg or MAP ≥60 mmHg
- urine output ≥0.5cc/kg/hr
- may use dopamine or dobutamine for BP
- may use lasix or mannitol for u/o
- may use atropine, dopamine, or low-dose epinephrine for bradycardia } pacemaker if no response

What are the principles of deceased donor organ retrieval?

- adequate exposure
- control of vessels above and below organs to be removed
- initiation of preservation in situ
- removal of organs
- separation of organs
- completion of preservation
- removal of histocompatibility specimens
- removal of iliac vessels for vascular reconstruction of pancreas and liver grafts
- organ packaging

KIDNEY PRESERVATION

What is involved in reperfusion injury after warm ischemic injury?

- Na-K pump impaired from lack of ATP
- results in NaCl and water passively diffusing into cells
- cellular swelling occurs, leading to the “no-flow” phenomenon after renal revascularization
- activation of lysosomal enzymes also leads to cell death
- during reperfusion, hypoxanthine (byproduct of ATP degradation) is oxidized to xanthine + free radical species, leading to further cell damage

What agents have been used in flush solution to minimize ischemic injury?

→ **hypothermia significantly reduces cellular energy requirements**

- use of hyperosmolar solution w/ impermeant solutes } eg mannitol, lactobionate, raffinose, hydroxyethyl starch
} prevents cell swelling when Na-K pump is impaired
- CCB
- xanthine oxidase inhibitors
- free-radical scavengers
- vasoprotective agents
- lysosomal stabilizers

What are the 2 basic methods of kidney preservation?

- 1) pulsatile machine perfusion with protein-based solution
 - better for kidneys exposed to long warm ischemic times
 - may have role in non-heart-beating donors } preserves grafts for ~72hrs
- 2) hypothermic flushing + simple cold storage
 - provides equivalent results for graft survival
 - slightly higher rate of delayed graft function

What are the components of UW solution?

- lactobionate, raffinose, and hydroxyethyl starch } impermeant solutes prevent cell swelling
- phosphate } acid buffer
- adenosine } for ATP synthesis
- glutathione } free radical scavenger
- allopurinol } xanthine oxidase inhibitor (reduces free radicals)
- Mg and dexamethasone } membrane-stabilizing agents

What are the advantages of UW solution over Euro-Collins solution?

- Euro-collins } glucose + Mg sulfate + K phosphate, Na bicarbonate (hypertonic)
- can be used for all intra-abdominal organs
- contains adenosine
- more rapid reduction in post-Tx serum creatinine
- lower post-Tx dialysis rate
- 6% higher 1yr graft survival rate } better 10yr graft survival rates

What is the management of a renal graft dropped on the floor?

- pick up organ immediately and assess for viability/damage
- irrigate entire graft with ABx solution
- inform recipient and discuss risks
- triple Abx for recipient and monitor for infection

RECIPIENT SELECTION FOR DECEASED DONOR KIDNEY TRANSPLANTS

What factors put you higher on the deceased donor waiting list?

- age <18yrs
- high panel reactive antibody (PRA) levels } probability of finding crossmatch-negative kidney is lower
- prior vital organ donation
- time on waiting list
- histocompatibility between donor and recipient

PRE-OP ASSESSMENT

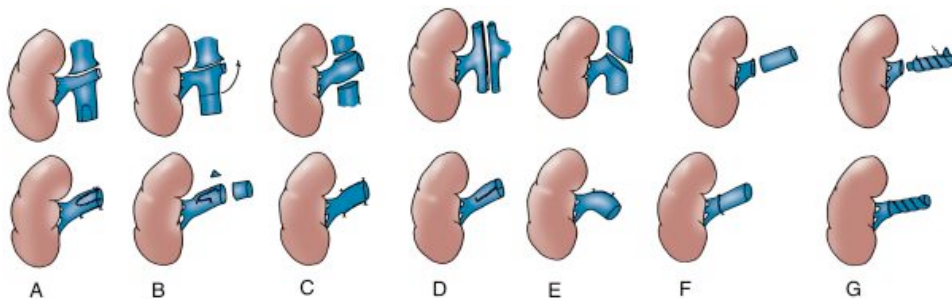
What is involved in the pre-op assessment prior to DD renal Tx?

- history and P/E } interval medical problems
 - } symptomatic cardiac disease
 - } active infection
 - } need for additional crossmatch due to recent transfusions
- immunosuppression protocol
- infection prophylaxis protocol
- need for dialysis

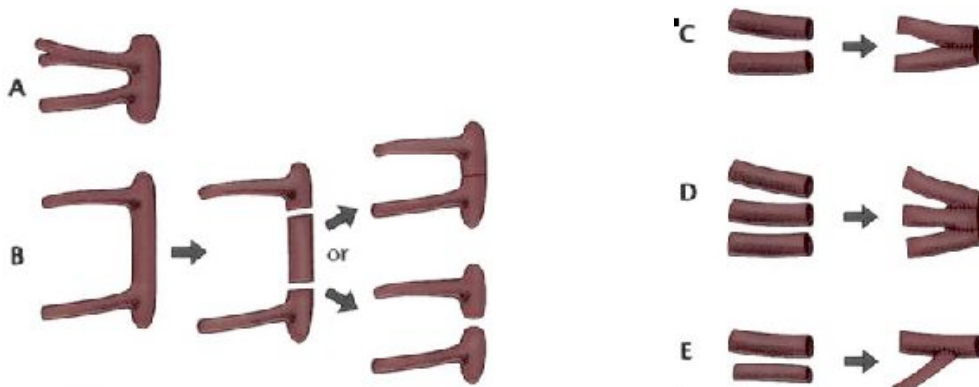
PREPARATION OF KIDNEY GRAFT

What are the techniques used to extend a short R renal vein?

→ can use IVC or donor external iliac vein



What are the techniques used to manage multiple renal arteries in donor kidneys?



RECIPIENT OPERATION

Which side is the ideal location for the renal graft?

- contralateral iliac fossa } allows renal pelvis & ureter to be medial and anterior
- in obese patients R side preferred } more superficial iliac veins
- in combined KP transplant, L side is preferred } left kidney (with long left renal vein)
- in small patients R side preferred } more room w/ wider choice of vessels for reanastomosis

What are the potential sites of arterial anastomosis for a renal graft?

- side of external iliac
- end of internal iliac } not an option if contralateral internal iliac has been used for prior Tx
- common iliac
- aorta
- native renal artery
- splenic artery

What agents are used to decrease arterial spasm during renal Tx?

- verapamil (CCB)
- papaverine (PDE inhibitor)
- adenosine

What are the advantages of an extravesical ureteroneocystostomy?

- faster
- doesn't require a separate cystotomy
- less ureteral length required } ensures better distal ureteral blood supply

What are the indications for a UU and pyeloureterostomy in renal Tx?

- short or ischemic allograft ureter \
- very limited bladder capacity } routine use of stents decreases complication rate
- surgeon's preference /

What intra-operative steps minimize ureteral complications during renal transplant?

- maintain blood supply to ureter, specifically "golden triangle" (hilum, gonadal vein, LP)
- maintain any LP arteries
- do not skeletonize ureter
- minimize handling
- tension free anastomosis
- spatulate
- kink free
- place stent
- place drain
- extravesical reimplant } can use shorter ureteric segment

List beneficial actions of mannitol

- osmotic diuresis } keeps tubules flushed free of casts
- free radical scavenger } prevents reperfusion injury
- prevents cell edema
- protects mitochondrial function
- increases RBF/GFR
- decreases intra-renal vascular resistance

POST-OP CARE

What are the options for fluid and electrolyte management post renal Tx?

- 1) 1/2 NS in 5% dextrose at 125-200cc/hr + occasional fluid boluses for hypoTN
- 2) 1/2 NS in 5% dextrose to replace insensible losses + 1/2 NS at same rate as previous hr's u/o
→ monitor serum lytes q4-8hrs post-op
→ if DGF, ensure CVP of ~10-15 cm H2O then try to use lasix to induce diuresis

What are the indications for U/S after renal Tx?

- DGF
 - ipsilateral leg swelling
 - ipsilateral abdominal swelling
 - decreased HgB
- \ / consider nuclear renal scan if
/ oligoanuria develops or if urine leak
/ suspected

What is the management of the urethral catheter post renal Tx?

- removed within 1 week } cystogram optional
- urine C&S prior to removal } if +ve, treat for 10-14days

What is the management of the ureteric stent post renal Tx?

- removed 6-12 weeks post-op } cover with prophylactic ABx

RENAL ALLOGRAFT REJECTION

What are the 2 histocompatibility systems important in renal Tx?

- 1) **ABO blood group** } patient has Ab's to RBC Ag's they lack
→ can plasmapheresis to remove anti-A & anti-B Abs prior to ABO mismatch Tx
- 2) **MHC** } MHC Ag's are encoded by MHC genes on **chromosome 6**
 - } **Class I antigens** are present on almost all nucleated cells (**except sperm**)
→ **HLA-A, HLA-B, HLA-C**
→ Ag's detected by tissue typing **T lymphocytes**
 - } **Class II antigens** are present on B lymphocytes, T lymphocytes, monocytes, macrophages, dendritic cells, and some endothelial cells
→ **HLA-DR, HLA-DQ, HLA-DP**
→ HLA-DR Ag detected by tissue typing of **B lymphocytes**
→ HLA-DQ and HLA-DP Ag's are not tested for
 - } **each person has two class I and one class II antigens from each parent**
→ **6 HLAs in total (HLA-A, HLA-B, and HLA-DR most important)**

*** HLA = human leukocyte antigen ***

*** crossmatch for ABO blood group + T lymphocytes + B lymphocytes ***

How are antigens recognized?

- T cells } see processed antigen (needs APC 2nd signal) → receptor is T cell receptor \ T cells DON'T
} activation produces cytokines → kills via cell surface molecules / activate
- B cells } see whole antigen (needs T cell cytokine signal) → receptor is Ab complement
} activation produces Ab → kills via complement fixation

What are the exceptions to incompatibilities that allow renal Tx?

- 1) **ABO** } A2 kidneys can be transplanted into O and B recipients
→ O and B have low anti-A2 Ab levels
} in rare cases of ABO incompatibility, recipient can undergo pre-Tx plasmapheresis to remove anti-A & anti-B Ab's + intense induction immunosuppression
- 2) **MHC** } if X-match can be rendered -ve by plasmapheresis + Ig administration, even +ve X-match recipient can receive Tx
→ **the more HLA Ag mismatches, the worse graft survival (best predictor)**
→ **DON'T DO Tx IF T CELL CYTOTOXIC +VE (Class I HLA), ok if B cell +ve**

What is the effect of MHC incompatibility?

→ **incompatibility with MHC Ag's on donor tissue stimulates immune response**

- class II antigens (on donor dendritic cells) can directly stimulate recipient CD4+ helper T cells
- class II antigens (via recipient macrophages) can also indirectly activate CD4+ helper T cells via a co-stimulatory 2nd signal

What is the result of CD4+ helper T cell activation?

→ **CD4+ helper T cell (Th) activation results in cytokine production**

→ **2 types of Th cells**

- Th1 cells produce type 1 cytokines } IFN- γ and TNF- α
- Th2 cells produce type 2 cytokines } IL-3, IL-4, IL-5, IL-6, IL-9

What is the result of IL-2 (cytokine) secretion?

→ **activated CD4+ helper T cells secrete cytokines (eg IL-2) via calcineurin activation**

- 1) maturation of CD8+ cytotoxic T lymphocytes
→ direct cytotoxicity
- 2) proliferation of B lymphocytes
- 3) stimulates release of other lymphokines (IL-3, IL-4, IL-5, IL-6, IFN- γ)
→ IL-3 is a growth factor for BM stem cells
- 4) B lymphocyte maturation into plasma cells
→ via IL4, IL-5, IL-6
→ plasma cells produce cytotoxic Ab's
→ complement-mediated damage + Ab-dependent cell-mediated cytotoxicity
- 5) activation of macrophages and NK cells } delayed type hypersensitivity
→ via IFN- γ

What are the different types of rejection?

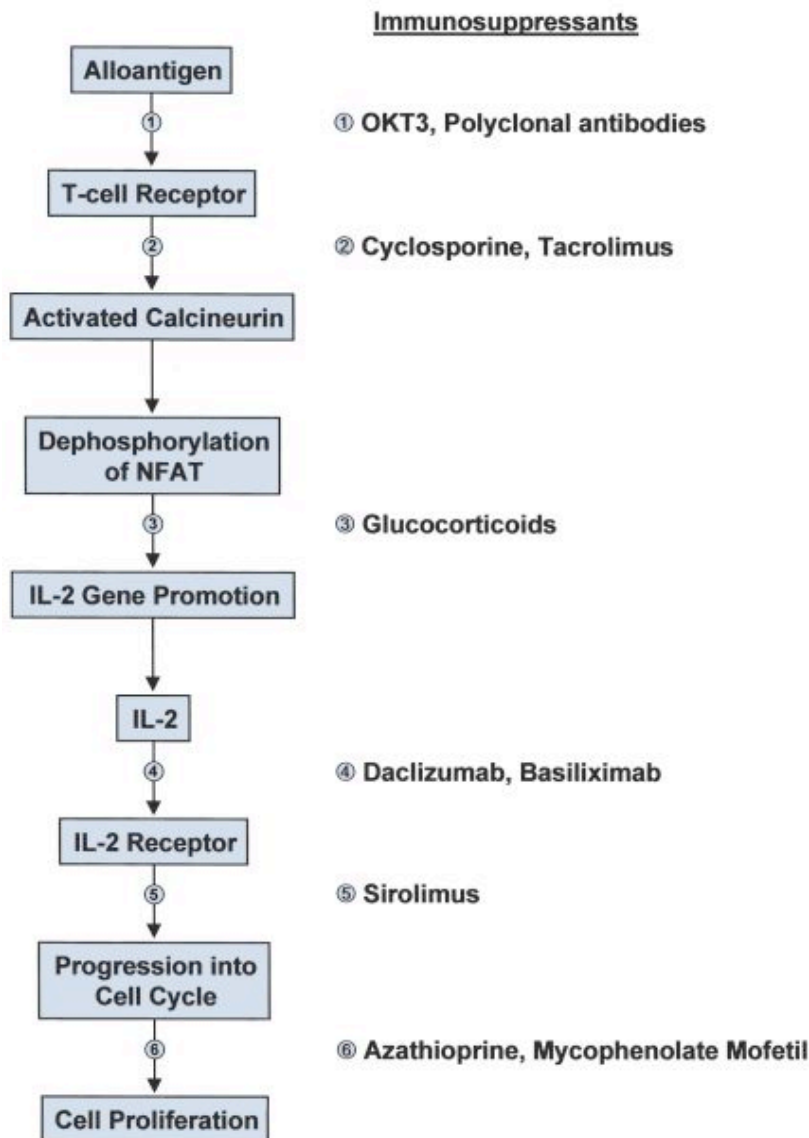
- 1) hyperacute
 - immediately after renal revascularization } **irreversible**
 - **mediated by pre-formed circulating cytotoxic Ab's (humoral)**
 - very rare if T cell and B cell crossmatch is negative
- 2) accelerated
 - occurs within days to weeks
 - often doesn't respond to anti-rejection meds
 - **mediated by humoral (Ab) & cellular components**
- 3) acute
 - can occur at any time after Tx } use Banff criteria to classify
 - presents with 'flu-like' symptoms, pain over enlarged graft, HTN, decreased u/o, fluid retention, increased creatinine, and decreased RBF, GFR and tubular function
→ **must r/o acute pyelo**
 - ?mediated by humoral & cellular components
 - Bx shows evidence of **mononuclear cellular infiltration, tubulitis, and vasculitis**
- 4) chronic
 - gradual decline in renal function associated with **interstitial fibrosis, vascular changes, & minimal mononuclear cell infiltration**
 - +ve B-cell or +ve flow crossmatch against donor B or T cells may predict development of development of chronic rejection

How do you classify acute rejection?

- Banff I } tubulitis (cellular damage only)
→ pulse steroids effective in 80%
- Banff II } tubulitis + glomerulitis (resistant to steroids) \ → thymoglobulin
- Banff III } arteritis, thrombosis, interstitial hemorrhage / → plasmapheresis if Ab present
→ IVIG, anti-B cell Ab preparations

What are the different types of immunosuppressive medications (CHART)?

- 1) steroids
 - glucocorticoids } reduces transcription of cytokine genes
- 2) calcineurin inhibitors
 - tacrolimus (Prograf, FK507) } inhibits calcineurin and IL-2 production
 - cyclosporine (Neoral) } inhibits calcineurin and IL-2 production
- 3) purine antagonists
 - mycophenolate mofetil (MMF/Cellcept) } inhibits purine synthesis
 - azathioprine (Imuran) } inhibits purine synthesis
- 4) IL-2 receptor blockers
 - sirolimus (rapamycin) } inhibits cell cycle progression
 - basiliximab (simulect) } blocks IL-2 receptor
- 5) anti-lymphocyte Ab preparations
 - monomurab CD3 (OKT3) } depletes T lymphocytes (?early inactivation)
 - equine anti-thymocyte globulin } depletes T lymphocytes
 - rabbit anti-thymocyte globulin } depletes T lymphocytes



What are the common immunosuppressive regimes used for renal Tx?

- steroids + CNI (tacrolimus or cyclosporine) + purine antagonist (MMF or AZT)
 - steroids started high and tapered
 - may add anti-lymphocyte Ab preparation (OKT3, RAT, etc)

How do the different immunosuppressive medications work (CHART)?

- 1) interferes with intracellular signaling
 - glucocorticoids
 - tacrolimus
 - cyclosporine
 - basiliximab
- 2) interferes with lymphocyte proliferation
 - MMF
 - azathioprine
 - sirolimus
- 3) interferes with Ag recognition
 - OKT3
 - equine anti-thymocyte globulin
 - rabbit anti-thymocyte globulin

What are the common S/Es of the common immunosuppressive meds?

- 1) steroids
 - HTN
 - DM
 - wt gain
 - poor wound healing
 - cushingoid features
 - AVN of hip
 - osteoporosis
 - hyperlipidemia
 - skin atrophy
 - striae
 - cataracts
 - acne
 - infections
- 2) tacrolimus (Prograf/FK506)
 - HTN
 - H/A
 - **DM**
 - diarrhea
 - **neurotoxicity**
 - **tremor**
 - nephrotoxicity
 - **hypoPO4**
- 3) cyclosporine (Neoral)
 - **HTN**
 - DM
 - **hyperlipidemia**
 - **hyperplasia of gingiva**
 - hyperK
 - hyperuricemia
 - neurotoxicity
 - nephrotoxicity
 - **hirsutism**
 - hepatotoxicity
 - hypoMg
 - **malignancy (lymphoma)**
- 4) azathioprine (Imuran)
 - **leukopenia**
 - hepatitis
 - **cholestasis**
 - **thrombocytopenia**
 - pancreatitis
 - **malignancy**
- 5) MMF (Cellcept)
 - **BM suppression**
 - malignancy
 - **N/V/D**
 - HTN
- 6) sirolimus (rapamycin)
 - **hyperlipidemia**
 - leukopenia
 - lymphocele
 - thrombocytopenia
 - **poor wound healing**
 - peripheral edema

***** BM myelosuppression NOT COMMON with CNIs *****

What are the main differences in calcineurin inhibitors?

→ tacrolimus & cyclosporine

- similar cost but **Tacrolimus may be slightly better in preventing acute rejection**
- both metabolized by CYP-450
- slightly different S/E profile } **tacrolimus has less HTN, hyperlipidemia, no hirsutism, and less issues with secondary malignancies**
 } **new onset DM & neurotoxicity (tremors) slightly more common with tacrolimus**
 } **HUS recurrence more common with cyclosporine**

What are the medications that interact with calcineurin inhibitors (CHART)?

→ decreases levels

- rifampin
- dilantin
- phenobarbitol
- INH
- carbamazepine

→ increases levels

- clarithromycin
- **diltiazem**
- **ketoconazole**
- clotrimazole
- methylprednisolone
- **erythromycin**
- verapamil
- fluconazole
- cimetidine
- metaclopramide

diltiazem and ketoconazole used to reduce dosing and cost

→ nephrotoxic synergy

- ketoconazole
- gentamicin
- cisplatin
- ranitidine
- amphotericin B
- vancomycin
- cimetidine
- diclofenac

What are the main differences in purine antagonists?

→ MMF & azathioprine

- MMF more effective
- MMF more toxic and more expensive

What is the management of acute rejection?

- high-dose pulse steroids
- if steroid-resistant rejection, use anti-lymphocyte Ab meds eg. muromonab CD3 (OKT3)
- changing one baseline immunosuppressive regime to another may help also

What is the treatment of AB-dependent rejection?

- IV Ig
- splenectomy
- plasmapheresis
- rituximab (anti-B cell Ab)

What post-op prophylactic medications are commonly used (CHART)?

- UTI } Septra or nitrofurantoin
- pneumocystis pneumonia } Septra
- oral candidiasis } clotrimazole lozenges
- vaginal candidiasis } clotrimazole vaginal inserts
- Herpes simplex virus } acyclovir
- CMV } gancyclovir
- peptic ulcer disease } H2 receptor blocker + antacid

PROBLEMS

What are the complications of renal transplantation?

- 1) Rejection
 - hyperacute
 - accelerated
 - acute
 - chronic
- 2) Vascular
 - vascular injury
 - kinking of renal artery/vein
 - thrombosis } renal graft, renal artery, renal vein
 - renal artery stenosis } due to atheroma, bad technique, clamp trauma, immunologic mechanisms
 - treat w/ PTA +/- stent
 - AV fistula
 - bleeding
 - lymphocele
 - perc drainage, sclerosis, marsupialization
 - renal allograft rupture
 - usually due to acute rejection or renal vein thrombosis
 - requires repair w/ bolstered mattress sutures, topical thrombotic agents, synthetic glue and mesh wrap
- 3) GU
 - ED
 - urinary extravasation
 - hematuria
 - treat w/ CBI, endoscopy w/ de clotting, fulgurization
 - obstruction
 - ureteric necrosis, slough, leak
 - UTI
- 4) GI
 - peritoneal/bowel injury
 - bowel obstruction
 - gastritis
 - pancreatitis
 - appendicitis
 - PUD
 - colonic perforation
- 5) Cancer
 - skin cancer
 - PTLN } NHL
 - Kaposi's
 - cervical carcinoma
 - renal tumours
 - carcinomas of vulva and perineum
- 6) Endocrine
 - new onset DM 2° to steroids, calcineurin inhibitors
- 7) Infections
 - immunocompromised
 - CMV, BK virus

→ “GIVE U Real Complications” } GI, Infections, Vascular, Endocrine, Urinary, Rejection, Cancer

What is the DDx of early delayed graft dysfunction (DGF)?

- 1) pre-renal } dehydration
 } hyperglycemia
 } vascular obstruction (renal artery or vein thrombosis)
 - 2) renal } severe ATN
 } rejection
 } calcineurin nephrotoxicity (usually preserves urine output)
 } infection
 } recurrence of prior disease
 - 3) post-renal } urinary obstruction (stone, clot, compression by lymphocele)
 } blocked catheter
- Rx → ABCs + vitals
 → irrigate catheter + hydrate
 → check BS & CNI levels
 → urinalysis & urine C&S
 → renal U/S
 → renal Bx

How do you differentiate CNI toxicity from acute rejection (CHART)?

CNI toxicity	acute rejection
- no fever	- fever
- u/o usually maintained	- decreased u/o
- no tenderness	- graft tenderness
- stable size	- enlarged graft
- slow rise in creatinine	- rapid rise in creatinine
- elevated CSA/tacrolimus levels	- N or low CNI levels
- normal Bx	- cellular infiltration, vasculitis, tubulitis on Bx

Table 40-13 -- Sorting Out Early Graft Dysfunction

Cause	Physical Finding	Initial Diagnostics Based on Suspicion
Infection	Fever, chills, normal or ↓ BP, ± pulmonary findings, ± native or kidney transplant tenderness	Chest radiograph, urinalysis, smears and cultures of sputum, urine, wound drainage, and blood; ultrasonogram of abdomen and kidney graft
Rejection	± Fever, normal or ↑ BP, normal or ↑ CVP, kidney transplant tenderness	Ultrasound of kidney graft, allograft biopsy
Obstruction	Vital signs normal unless infected, ± kidney transplant tenderness	Irrigate bladder catheter, ultrasound and Doppler flow study of kidney graft
Calcineurin inhibitor toxicity	Afebrile, normal or ↑ BP, normal CVP, ± tremor	Calcineurin inhibitor blood level
Hyperglycemia	Afebrile, ↓ BP, ↓ CVP	Blood sugar
Dehydration	Afebrile, ↓ BP, ↓ CVP	IV fluid bolus

What are the potential vascular complications of renal Tx?

- kinking of artery or vein
- thrombosis } may occur due to hyperacute rejection or thrombophilia
- RAS } presents with difficult to manage HTN +/- impaired renal function
 } due to **atheroma, bad suture technique, clamp trauma, or immunologic mechanisms**
 } giving ACE inhibitor causes creatinine to rise
 Rx → PTA +/- endoluminal stent placement
- graft rupture } due to acute rejection or renal vein thrombosis
 Rx → requires immediate OR
 → if from RV thrombosis, graft usually lost

What are the indications for Tx nephrectomy?

- 1) symptomatic irreversibly rejected graft
 - 2) to withdraw immunosuppression in asymptomatic chronically rejected graft
 - 3) to prevent development of anti-HLA Ab's in asymptomatic chronically rejected graft
- becomes very difficult after 4-6 weeks from time of Tx
- } dense fibrous reaction
 - } may need to do subcapsular Nx
 - } ureteral stump left behind
- **can withdraw CNIs immediately**
- **MMF, azathioprine, sirolimus are continued for another 4 weeks**
- **must taper steroids over 2-6 weeks (depends on length of steroid therapy)**

What is the cause of hematuria post-renal Tx?

- early } catheter trauma
 - } urinary tract reconstruction
 - Rx → conservative mgt
 - cysto + fulguration if persistent
 - surgical exploration if still refractory
- late } medical renal disease in graft
 - } infection
 - } stone
 - } malignancy
 - Rx → standard hematuria work-up
 - try to avoid CBI if possible } risk of pyelonephritis

What is the Ddx of a post-Tx perinephric fluid collection?

- **most are incidental findings that need no Rx**
- blood
 - urinoma (high creatinine)
 - infection (WBCs, bacteria, purulent)
 - lymphocele (clear, serum creat, elevated TGs and milky if chylous)
 - seroma

What is the management of a perinephric fluid collection?

- 1) observe if not symptomatic
- 2) aspiration if hydronephrosis, unexplained fever, pain, ipsilateral leg swelling
 - drain if pus } usually will need open drainage
 - **start ABx**
 - **continue CNIs & steroids (at lower dose)**
 - **stop MMF, azathioprine, sirolimus**
 - repeat U/S after aspiration for others
 - observe if no recurrence
 - recurrence of blood } explore
 - recurrence of lymphocele } open or lap unroofing/marsupialization
 - } percutaneous sclerosis (especially if lateral)
 - } if infected, drain first (can't marsupialize if infected)
 - recurrence of urine } open surgical repair after CT cystogram +/- IVP
 - reimplant
 - native ureter to donor renal pelvis
 - Boari to renal pelvis
 - Transplant Nx

What are the RFs for lymphocele development?

- heparin use
- obesity
- sirolimus use

What are the non-surgical causes of a post-Tx lymphocele? } } } “ Real BAD PASS”

- Rejection (acute)
- Bx
- AV fistula
- Diuretic use
- PCKD
- Anticoagulants use (high dose)
- Steroid use (high dose)
- Sirolimus use

What is the DDx of post-Tx hydronephrosis?

→ investigated with U/S + nuclear scan

- early } technical error (usually needs revision)
 - } edema (usually resolves within a few days)
 - } blood clot (usually lyse with natural urokinase)
 - } unsuspected donor stone
 - } perinephric fluid collection
- late } periureteral fibrosis
 - } stones
 - } tumour
 - } fungus ball
 - } lymphocele
 -) BK-related polyomavirus nephropathy
 -) chronic ischemia w/ stricture
 - Rx → percutaneous dilation if short
 - reimplant if long or if proximal/mid ureter
 - if stricture is too long may need UU, ureteropyelostomy or vesicopyelostomy or vesicocalycostomy or ileal ureter

What are the causes of stones post-renal Tx?

→ WILL NOT have renal colic (denervation) } presents w/ hematuria or acute rise in creatinine

- persistent secondary hyperPTH'ism
- recurrent UTIs
- FB (suture or staple)
- obstruction
- habitual decreased fluid intake
- distal RTA (CaPO₄ stones)

Rx → PNL, SWL, ureteroscopy are all options } ureteroscopy may be difficult

What are some common GU tract infections associated with renal Tx?

→ UTIs occur in up to 40% } associated with increased mortality after renal Tx

- bacterial } prophylactic Septra for first 3 months
 - } late UTIs are usually benign and respond to conventional Abx
 - } if pyelo develops, screen with U/S for obstruction or stone
 - need to r/o acute rejection
- candida cystitis } often responds to FB removal and bladder irrigation with amphotericin B
 - } +/- oral fluconazole
 - need to reduce CNI dosage if fluconazole given
 - } iv fluconazole or amphotericin if tissue-invasive infection
- adenovirus } can lead to hemorrhagic cystitis
 - } usually self-limited and resolves within 1-2 weeks
 - } hydration + diuresis
- BK polyomavirus } occurs in 10-45% of recipients
 - } can cause significant nephropathy in ~6% of infected recipients
 - } can mimic acute rejection
 - } diagnosed by PCR of urine or blood → Bx often inconclusive
 - } reduction of immunosuppression, antiviral therapy (eg cidofovir)

What are the RFs for UTI in renal Tx patients?

- immunosuppression
- foley
- advanced age
- use of deceased donor kidney
- females
- DM
- pre-existing GU tract abN'ity

How does Septra (TMP/SMX) affect serum creatinine?

- can increase Cr level
- due to interference of tubular secretion of Cr

What are the potential causes of ED after renal Tx (CHART)? } } } "SCANT Erections"

- Smooth muscle (cavernosal) dysfunction
 - DM
 - CNI
 - hypercholesterolemia
- Central effects
 - anti-HTNsives
 - anxiety
- Arterial supply reduced
 - renal artery anastomosis } internal iliacs
 - accelerated arteriosclerosis } prednisone, cyclosporine, DM, propranolol
 - anti-HTNsives, diuretics
- Neurogenic cause
 - DM
 - uremia
- Tunica albuginea dysfunction
 - propranolol (Peyronie's)
- Endocrine problems
 - ↓'d Testosterone (cyclosporine, sirolimus)

What are the management options for ED after renal Tx (CHART)? } } } "Lets Make A VIP Virile"

- 1) Lifestyle/psychotherapy/counseling } stop EtOH, stop smoking, alternate sexual techniques
- 2) Medication changes } use CCB, ACEI instead of β -blockers
 - } use ranitidine, famotidine instead of cimetidine
 - } stop steroids if possible
- 3) Add medications } testosterone, T4 replacement, PDE5-I
- 4) Vacuum devices
- 5) ICI } PGE1
 - slightly higher risk of infection
- 6) Penile prostheses } malleable, inflatable (avoid prevesical reservoir)
 - higher risk of infections
- 7) Vascular procedures } angiodilation, revascularization

List differences in management of ED in a transplant patient

- "Change (PCA) DRIP"
- Change meds (stop Prednisone, Cimetidine, Anti-HTN'sives)
- Dose adjust PDE-5 inhibitors } if graft dysfunction or on cimetidine, ketoconazole, CsA, etc
- Revascularization if anastomotic issue
- Infection risk higher for ICI and penile prosthesis
- Perivesical reservoir contraindicated

What are the pre-requisites necessary for penile prosthesis insertion after renal Tx?

→ “My RIGID PP”

- **Minimize** tissue dissection
- **Rejection** free for ≥ 6 mos
- **Infection** free (skin or urine)
- **Graft** function stable
- **Immunosuppressants** at lowest possible doses
- **Device** with low probability of malfunction
- **Prophylactic Abx** for 2wks post-op
- **Perivesical** reservoir contraindicated

What is the effect of renal Tx on fertility?

→ men

- improvement of erections
- normalization of FSH, LH, and T levels
- spermatogenesis improves
- no evidence of increased congenital abnormalities } **should delay impregnation for at least 1yr after Tx**

→ women

- restores fertility in pre-menopausal women
- spontaneous pregnancy in 60%
- 95% successful pregnancy if you make it past T1 } **no increased risk of abN’ites**
- Tx kidney rarely causes dystocia
- **higher rate of preterm deliveries (50%)**
- higher rate of pregnancy-induced HTN (30%) and IUGR (20%)
- no effect on rejection } 10%, same as non-pregnant

What are the guidelines for successful pregnancy after renal Tx?

- good general health for 2yrs after Tx
- minimal proteinuria
- no HTN
- no rejection
- no urinary tract obstruction
- nearly normal renal function
- on low dose maintenance immunosuppression

Which immunosuppressive medications are safe during pregnancy (CHART)?

- no fetal risk in animal studies (no RCTs) (class B)
 - basiliximab
- cannot rule out fetal risk (class C)
 - steroids
 - MMF
 - CNIs
 - sirolimus
 - OKT3
- evidence of increased fetal risk (class D)
 - **azathioprine**

What are the common causes of pneumonia in renal Tx patients?

- usually due to common bacterial pathogens
- also due to Legionella, Nocardia, mycobacteria, viruses, Pneumocystis (parasites), fungi

What is the risk of malignancy after renal Tx? }} “SLK, Really Vain Car”

- higher rate of malignancy than general population, especially;
 - non-melanoma **S**kin cancers (most common)
 - NH **L**ymphoma (B cell)
 - **K**aposi’s sarcoma
 - **RCC**
 - **V**ulvar and **C**ervical Ca

What are the long term cardiovascular risks associated with renal Tx?

- nonsurgical HTN common after Tx } meds (steroids, cyclosporine, tacrolimus)
 - } intrinsic renal disease
 - } rejection
- MI & stroke are common causes of death after Tx } steroids & CNIs cause hyperlipidemia
- new DM occurs in significant % of renal Tx recipients } diabetogenic effects of steroids & CNIs

What are the RFs for graft hyperfiltration injury?

- small kidney into large recipient
- Tx from female donor to male recipient
- cadaveric Tx
- rejection
- systemic HTN
- hypercholesterolemia
- steroids
- obesity
- anti-HTN’sives
- diuretics
- high protein intake

What are the MOA and side effects of each immunosuppressant?

Drugs	Pros	Side effects
Corticosteroids		
Prednisone M: ↓ transcription of cytokine genes I: intracellular signaling	1. Cheap 2. 1 st line for acute rejection 3. May be required to prevent chronic rejection	1. DM 2. Avascular necrosis of hip 3. Osteoporosis 4. HTN 5. ↑ Lipid 6. Wt. gain 7. Appearance
Calcineurin Inhibitors		
Cyclosporine M: (-) calcineurin & IL2 production I: intercellular signaling	1. 20 years experience 2. Excellent graft survival in all solid organ transplants	1. hyper-tension (↑ vs. Tac) 2. hyper-lipidemia 3. hyper-glycemia 4. hyper-kalemia 5. hyper-chloremia 6. hyper-plasia of gingiva 7. HYPOmagnesemia 8. hepatotoxicity (cholelithiasis) 9. hirsutism (↑ vs. Tac) 1. neurotoxicity 2. nephrotoxicity 3. neoplasms (↑ vs. Tac) } skin } lip } cervix } NHL 4. no-erections 5. interaction w/ medications
Tacrolimus (Prograf) (FK 506) M: (-) calcineurin & IL2 production I: intercellular signaling	1. Less HTN 2. Less ↑Lipid 3. No hirsutism 4. Potentially less acute rejection 5. Better trough to AUC correlation 6. Rescue effect	1. HTN 2. DM / glucose intolerance (↑ vs. CSA) 3. neurotoxicity (↑ vs. CSA) 4. nephrotoxicity 5. interaction w/ medications 6. Still requires drug monitoring 7. Less experience 8. More infx (?)
Antimetabolites		
Azathioprine (Imuran) M: (-) purine synthesis I: lymphocyte proliferation	1. Inexpensive 2. Generally well tolerated 3. Questionable efficacy 4. worst Tx med for pregnancy	1. thrombocytopenia 2. leukopenia 3. hepatitis 4. cholestasis 5. pancreatitis 6. interaction with allopurinol
Mycophenolate (Cellcept) M: (-) purine synthesis I: lymphocyte proliferation	1. Used for acute rejection 2. May allow calcineurin inhibitor reduction or steroid withdrawal 3. more effective than Aza 4. Potent immunosuppressant 5. Optimal dosing unclear	1. BM suppression 2. N/V/D 3. Expensive 4. Longterm use controversial 5. NO: nephrotoxicity, neurotoxicity, hepatotoxicity

IL-2 Receptor Blockers (G1 → S inhibition)			
Sirolimus (Rapamycin, Rapamune) M: (-) cell cycle progression I: lymphocyte proliferation	1.	Potential synergy with CsA or FK506	1. hyperlipidemia (TG and cholesterol)
	2.	Not nephrotoxic	2. leukopenia
	3.	May allow calcineurin inhibitor sparing or elimination	3. thrombocytopenia
	4.	Good correlation of trough to AUC	4. poor wound healing
	5.	Alternative for rescue	5. interactions w/ CSA absorption and elimination so dose at different time
			6. Blood level monitoring
			7. Expense
IL-2 Receptor Blockers (anti-CD 25 mAb)			
Basiliximab (Simulect) Dazclizumab (Zenapax) M: block IL2 receptor I: intercellular signalings	1.	Long t 1/2 = simple dosing	1. Expensive
	2.	No 1 st dose effect	2. No trials in high risk pts
	3.	Few SEs	3. Questionable added benefit to triple tx with MMF
	4.	Acute rejection in low risk pts on double or triple tx with Imuran	
	5.	May allow steroid avoidance	
	6.	safest Tx med in pregnancy	
Antilymphocyte Ab			
ALG – ATG (Atgam) M: deplete T lymphocytes I: antigen recognition	1.	Induction	1. Ab soup – multiple specificities
	2.	Tx of rejection	2. Expensive
			3. Batch variation
OKT3 (muronomab CD3) M: deplete T lymphocytes I: antigen recognition	1.	Induction	1. 1 st dose reaction
	2.	Prophylaxis of rejection	2. HAMA
	3.	No batch variation	3. Potent immunosuppression
	4.	Can monitor	
	5.	Easy to use	

Chapter #41 – Renal Failure

ACUTE RENAL FAILURE

What is the definition of ARF?

- occurs in 2-5% of in-patients } occurs in 20-30% of ICU patients
- rapid reduction in renal function characterized by progressive azotemia
- **cardinal feature is a decline in GFR } best measured by rising serum creatinine**
- may or may not be accompanied by oliguria } occurs over hrs to days
- results in failure to excrete nitrogenous wastes, maintain N volume status & maintain lytes homeostasis

What is the relationship between BUN, creatinine, and GFR?

- BUN can be disproportionately elevated and may not accurately reflect GFR
 - dehydration → hypercatabolic states (trauma) → increased protein load (GI bleed, TPN)
- serum creatinine more accurately reflects GFR } although not perfect (cystatin C may be better)
- CrCl may overestimate GFR as renal function declines } secretion of creatinine

What is GFR?

- **reflection of overall renal function**
- determined by both **hydrostatic & oncotic pressure** (Starling's forces) differences between glomerular capillary and Bowman's space
- also affected by permeability of glomerular membrane
- **N in males is ~125 mL/min and N in females is 100mL/min**

What factors affect GFR?

- 1) **transglomerular pressure } most important factor**
 - depends on systemic BP & more so intraglomerular capillary pressure
- 2) RPF
 - increase in RPF leads to increase in GFR
- 3) glomerular permeability
 - reduction in permeability = reduction in GFR
 - increased permeability DOES NOT lead to increased GFR
 - glomerulus at max permeability to water/solutes already
 - does lead to increased filtration of larger molecules not normally filtered eg albumin
- 4) oncotic pressure } least important factor
 - normally, plasma proteins are not filtered so oncotic pressure within Bowman's space is ~0

How does the body regulate GFR?

→ **GFR is maintained relatively constant despite large fluctuations in systemic BP & RBF**

- 1) **autoregulation**
 - occurs likely related to stretch receptors (ATP-mediated) and AT II
 - rise in MAP causes constriction of **afferent arteriole**, and vice versa
 - **results in maintenance of intraglomerular capillary pressure**
 - MAP <70mmHg leads to decreased GFR
 - MAP <40mmHg leads to stoppage of filtration
- 2) **tubuloglomerular feedback**
 - macula densa senses ultrafiltrate levels (Na and Cl)
 - increased delivery of Na & Cl to distal tubule results in constriction of **afferent arteriole** & subsequent decrease in RPF
 - mediated by AT II via adenosine, TXA, NO effects on afferent arteriole

*** under abN conditions, however, neurohumoral responses become more important (NE & AT₂) ***

How do you measure GFR?

- can't be measured directly } 1) renal clearance eg inulin clearance, CrCl, etc
2) plasma markers eg creatinine, cystatin C, etc
3) formulae eg Cockcroft-Gault, MDRD, etc

→ normal GFR is ~ 100-120 mL/min/1.73m²

→ CrCl is an estimate of GFR (slight over-estimation due to secretion of creatinine)

→ normal creatinine clearance is ~120-140 mL/min

→ only valid in "steady state" NOT in ARF

1) Cockcroft-Gault

→ margin of error (up to 30%)

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{creatinine}} \times (0.85 \text{ if female})$$

2) 24hr urinary calculation

→ cumbersome

$$\text{CrCl} = \frac{\text{Urine [creatinine]} \times \text{urine flow rate}}{\text{Plasma [creatinine]}}$$

3) abbreviated MDRD study equation

→ often underestimates CrCl

$$\text{GFR} = [175 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203}] \times \begin{cases} 0.742 \text{ if female} \\ 1.210 \text{ if Black} \end{cases}$$

What are the causes of ARF (CHART)?

1) Pre-renal

→ reversible with Rx of underlying cause + lack of structural damage to the kidney

→ **due to reduction in RBF } activation of sympathetics and RAAS**

a) volume depletion } hemorrhage, dehydration, shock, N/V/D, etc

b) low ECFV } nephrotic syndrome, sepsis, liver failure, burns, crush injuries, bilateral RAS

c) cardiac } MI, CHF, aortic stenosis, tamponade, etc

2) Renal

a) ATN (most common nosocomial cause) } renal ischemia most common cause of ATN

} see **heme granular casts + renal tubular epithelial cells** on U/A

b) AIN } **most often drug-induced (NOT dose dependent)**

} also due to:

- sarcoidosis
- strept infection
- viral infection (CMV, EBV)
- Legionella

} often presents with fever, rash (25%), and recent medication (1-2weeks)

} **sterile pyuria + WBC casts + eosinophiluria + proteinuria (mild <1g/day)**

} get interstitial edema + marked interstitial infiltration of T lymphocytes & monocytes

c) acute GN } **proteinuria + hematuria + RBC casts** pathognomonic of GN

} if loss of renal function is rapid (days to months) then represents rapidly progressive glomerulonephritis (RPGN)

} specific therapies depend on cause of GN

→ steroids, cyclophosphamide, plasma exchange, etc

3) Post-renal

→ bilateral obstruction or unilateral obstruction of solitary functional kidney

→ partial obstruction may exist in presence of adequate U/O

- AUR
- stones
- MUO
- RPF

What is hepato-renal syndrome?

→ **severe form of pre-renal ARF**

- ARF in the setting of advanced liver disease (cirrhosis, mets, EtOH hepatitis)
- renal hypoperfusion due to relative **splanchnic vasodilatation** } **mediated by NO**
- characterized by **oliguria, benign U/A, low urine [Na], and progressive rise in creatinine**
- diagnosis of exclusion } must r/o ATN, acute GN, vasculitis, low ECFV

Rx → **improvement of liver function or liver Tx** } **best hope**

- ACEI, Mucomyst, midodrine + octreotide } **disappointing**
- survival often limited by liver failure
- HD often difficult due to hemodynamic instability

What are some of the medications known to cause AIN (CHART)? } } } “3C PORN ATLAS”

- Cephalosporins
- Cipro
- Cimetidine
- Penicillins
- Omeprazole
- Rifampin
- NSAIDs
- Allopurinol
- Thiazides
- Lasix
- ASA
- Sulfa

What is unique about AIN due to NSAIDs?

- usually NO fever, NO rash, NO eosinophilia
- proteinuria is usually severe not mild

What is the management of AIN?

- remove offending agent
- steroid or cytotoxic agents may help recovery of renal function
- usually improves in 3-7 days

What are the 3 types of idiopathic RPGN?

→ **based on renal Bx and serologic testing**

- 1) type 1 → anti-glomerular BM disease (eg. Goodpasture's syndrome)
- 2) type 2 → immune complex deposition disease (eg. SLE, post-streptococcal GN)
- 3) type 3 → pauci-immune (eg. ANCA +ve Wegener's granulomatosis)

What is the DDx of RPGN?

→ multisystem diseases

- | | |
|----------------------------|--|
| - SLE | - Goodpasture's disease |
| - Henoch-Schonlein purpura | - necrotizing vasculitis (incl. Wegener's) |
| - cryoglobulinemia | - neoplasia (colon, lung) |
| - Behcet's disease | |

→ superimposed on primary glomerular disease

- | | |
|----------------------------|-----------------|
| - membranoproliferative GN | - membranous GN |
| - IgA nephropathy | |

→ infectious disease

- | | |
|-------------------|---------------------------|
| - post-strept GN | - infectious endocarditis |
| - visceral sepsis | - Hep B or C infection |

→ drugs and toxins

- | | |
|---------------|-------------------|
| - allopurinol | - D-Penicillamine |
| - hydralazine | - rifampin |

→ idiopathic

ACUTE TUBULAR NECROSIS

What are the causes of ATN?

→ majority of nosocomial ARF is secondary to ATN

- 1) **renal hypoperfusion/renal ischemia** } **majority**
- 2) nephrotoxic insults

What are some nephrotoxic causes of ATN (CHART)?

- 1) endogenous nephrotoxins
 - myoglobin
 - uric acid
 - oxalate
 - plasma cell dyscrasias (eg MM)
- 2) exogenous nephrotoxins
 - **aminoglycosides**
 - **acyclovir**
 - **ACE inhibitors**
 - tacrolimus
 - **indinavir**
 - amphetamine
 - **cephalosporins**
 - vancomycin
 - **cisplatin**
 - IL-2
 - insecticides
 - enflurane
 - **Septra**
 - **contrast dye**
 - MTX
 - IFN
 - aniline dye
 - RADs
 - **amphotericin B**
 - **NSAIDs**
 - cyclosporine
 - cimetidine
 - heroin

What are the urinary findings of ATN?

- **heme granular casts**
- **renal tubular epithelial cells**
- **urine Na >40**
- **urine osmolality <400**
- **FENa >1**
- **urine-to-plasma Cr ratio <20**

What lab finding is suggestive of pigment nephropathy?

- eg myoglobinuria (rhabdomyolysis)
- **hematuria on dipstick BUT absence of RBCs on urine R&M**
 - often seen after urethroplasty (long duration in extended lithotomy) and lap donor Nx
 - combination of renal hypoperfusion + nephrotoxic insult of myoglobin/hemoglobin w/in PCT can result in ATN
 - Rx → forced alkaline diuresis

What is the natural hx of ATN?

→ **oliguric ATN vs non-oliguric ATN**

- 1) oliguric phase } starts <24hrs after inciting insult
 - } may last for 1-3 weeks (may be prolonged in elderly)
 - watch for metabolic abN'ities, GI bleeds, infection
- 2) diuretic phase } progressive increase in urine volume
 - } start of renal recovery
 - } creatinine may still rise for 24-48hrs before reaching a plateau then falling
 - watch for severe electrolyte and fluid abnormalities as well as infection
 - 25% of deaths with ARF occur in this phase
- 3) recovery phase } return of renal function towards baseline
 - } abN'ities in urinary [] & dilution may persist for wks or months

What is the pathophysiology of ischemic ATN?

- 1) **renal ischemia leads to depletion of ATP (sentinel event)**
 - a) AMP (metabolite of ATP) is further metabolized to adenosine, inosine, hypoxanthine
 - these metabolites diffuse out of cell, resulting in loss of substrate reservoir for ATP synthesis after reperfusion
 - hypoxanthine becomes substrate for O₂ free radical production
 - b) loss of ATP leads to impaired function of Na-K-ATPase, Na-Ca-ATPase
 - get activation of phospholipases that damage cell membrane
- 2) **oxidative stress during reperfusion** after ischemia is associated with cell damage
 - w/ reperfusion, accumulated hypoxanthine is converted to xanthine + O₂ free radicals
- 3) **RBF reduced by ≥50%**
 - outer medulla is most sensitive to ischemic injury (vasoconstriction + congestion of medullary vasculature by WBCs, RBCs, platelets)
- 4) **tubular cell injury** can be sublethal or lethal
 - a) loss of cell polarity \ get impaired solute and
 - b) redistribution of Na-K pumps and integrins / water transport
 - c) brush border loss \ get intratubule cast formation
 - d) loss in cell-matrix adhesion / with obstruction
 - e) loss of tight junction function } get backleak of glomerular filtrate
- 5) ischemia leads to **release of inflammatory mediators** (neutrophils, IL-8, lymphocytes)

CLINICAL APPROACH TO THE DDX OF ACUTE RENAL FAILURE

What is the approach to ARF?

- 1) history & physical
 - meds and other possible nephrotoxins
 - evidence of systemic disease
 - assess volume status
 - assess cardiovascular hemodynamics
 - assess previous renal function
 - check patency of catheters, stents, etc
 - check vitals and hemodynamic parameters
 - 2) labwork
 - compare to previous labs
 - urinalysis
 - urine microscopy
 - creatinine
 - urine lytes
 - FENa
 - 3) imaging
 - renal U/S (+/- Doppler)
 - renal scan (MAG-3 better than DTPA)
 - KUB (stones)
- **severe oligoanuria suggests post-renal cause, renovascular occlusion, or severe ATN**

What are some known RFs associated with ARF?

- advanced age
- contrast dye exposure
- ABx (aminoglycosides, etc)
- NSAIDs
- ACE inhibitors
- atheroembolism
- recent hemodynamic instability } surgical bleed, sepsis, etc
- comorbid conditions } CHF, liver failure, renal insufficiency, DM

Table 41-6 -- Urine Sediment in Acute Renal Failure

Sediment Findings	Diagnosis
Normal	Prerenal/obstruction
Red blood cell casts, red blood cells	Acute glomerulonephritis/vasculitis
Eosinophils	Acute interstitial nephritis
Pigmented granular casts	Acute tubular necrosis

How can urinary studies be used to delineate the cause of ARF (CHART)?

	Pre-renal or Acute GN	ATN or Obstruction
Urine [Na] mEq/L	<20	>40
Urine-to-plasma creatinine	>30	<20
FE _{Na}	<1%	>1%
Urinary osmolality	>500	<400
Renal Failure index	<1	>1

How do you calculate FE_{Na} ?

→ fractional excretion of Na

$$- \text{FE}_{\text{Na}} = \frac{U_{[\text{Na}]} \times P_{[\text{creat}]}}{P_{[\text{Na}]} \times U_{[\text{creat}]}} \times 100\%$$

How do you calculate RFI?

→ renal failure index

$$- \text{RFI} = \frac{U_{[\text{Na}]} \times P_{[\text{creat}]}}{U_{[\text{creat}]}}$$

What type of renal scan is most useful in ARF?

- MAG3 } can evaluate both renal flow AND function

→ DTPA (100% filtration) not good for renal failure or renal immaturity (kids)

MANAGEMENT OF ACUTE RENAL FAILURE

What are the potential complications of ARF (CHART)?

→ fluid overload

- HTN

- acute pulmonary edema

- edema

→ electrolyte abnormalities

- hypoNa

- hyperK

- hyperMg

- hyperPO₄

- hypoCa

- hyperCa (post-rhabdo)

- hyperuricemia

- metabolic acidosis

→ uremic signs and symptoms

- N/V

- upper GI bleed

- encephalopathy

- seizures/coma

- pericarditis

- uremic cardiomyopathy

- pleuritis

- bleeding

- impaired immune function

- neuropathy

What are the goals of management of ATN?

- prevent further renal injury
- preventing complications
- providing environment conducive to renal recovery
- if possible, convert oliguric ATN to non-oliguric ATN
- ensure adequate nutrition

What meds have been used to decrease morbidity of ATN?

- 1) loop diuretics (eg lasix) } induces diuresis to wash out obstructive debris and casts
 } decrease energy requirements in TAL
 } use may increase u/o but has little effect on outcome of ARF
 → early use peri-insult can decrease degree of renal injury
- 2) mannitol } induces diuresis to wash out obstructive debris and casts
 } reduces hypoxic cell edema (osmotic)
 } increases RBF
 } free radical scavenger
 } protects mitochondrial function
 → prophylactic or early use may be beneficial
- 3) dopamine } selective renal vasodilator
 } induces natriuresis and increased u/o
 → no good evidence demonstrating benefit } may have small role
- 4) fenoldopam } selective dopamine-1 receptor agonist
 } increases RBF and decreases renal vascular resistance
 → no good evidence demonstrating benefit
- 5) intrarenal arterial infusion of ANP } vasodilatory action
 → still investigational } may have role in oliguric ATN
- 6) growth factors (eg IGF-1, EGF) } accelerating recovery of renal tubules
 → no good
- 7) CCBs (eg verapamil) } reverse vascular constriction
 } increase GFR and improve renal plasma flow
 → evidence showing benefit for renal Tx recipients

What is the conservative medical management of ATN (CHART)?

→ once diagnosis is made, conservative medical management

- 1) fluid balance
 - monitor ins and outs
 - restrict fluids
- 2) electrolytes and acid-base balance
 - prevent and treat hyperK
 - avoid hypoNa
 - keep bicarb >15 mEq/L
 - minimize hyperPO₄
 - treat hypoCa (if symptomatic)
 - watch for hyperMg
 - watch for hyperglycemia (insulin resistance)
- 3) uremia and nutrition
 - moderate (not restricted) protein intake (1g/kg/day) and maintain caloric intake
 - minimize carbohydrate intake (≤ 100 g/day)
- 4) meds
 - review all meds
 - renal dosing for meds
 - stop Mg-containing meds

What are the EKG findings of hyperK?

- loss of p wave
- widened QRS
- **peaked T waves (earliest sign)**
- sine wave (just before death)

What are the 3 main goals in the treatment of hyperK?

- 1) stabilize electrical membrane of cardiac conducting system } Ca gluconate
- 2) shift K back into cells } insulin, NaHCO₃, ventolin
- 3) eventually eliminate K from body } lasix, kayexalate

What are the indications for dialysis? } “OK PUMP”

- volume **O**verload (pulmonary edema)
- severe hyper**K**
- uremic **P**ericarditis
- symptomatic **U**remia (eg encephalopathy, neuropathy)
- severe **M**etabolic acidosis
- selected **P**oisonings (dialyzable toxin)

What are the theoretical mechanisms by which dialysis may worsen ARF from ATN?

- 1) fall in urine output
- 2) dialysis-induced hypoTN
- 3) complement activation from blood-dialysis membrane interaction

What are the different types of RRT for ARF?

→ **no significant difference between IHD and CVVHD**

→ **CVVHD might have slightly lower mortality rate**

- 1) IHD } standard modality of dialysis
} can have significant hemodynamic complications
→ hypoTN, hypoxia, bleeding from anticoagulation, dialysis disequilibrium syndrome (cramps, headaches, seizures, coma)
- 2) CVVHD } continuous veno-venous HD
} slow fluid and solute removal for hemodynamically unstable patients
} as effective as IHD over the course of 24-48hrs
- 3) PD } less efficient but also less hemodynamically stressful

Does type of dialysis membrane affect outcome?

→ **no significant difference between types of dialysis membranes**

→ **high-flux membranes have no survival benefit**

- 1) cellulose-derived membrane
- 2) non-cellulose-derived membrane } synthetic polymer
} more biocompatible but more expensive

Does dose of dialysis affect outcome?

- daily HD improves mortality rate in some studies } ?related to urea levels

What is the prognosis of ATN?

→ **prognosis depends on underlying 1° disease that caused ARF and if complications arise**

- mortality rate is ~50%
- 25% complete recovery
- 20% incomplete recovery
- 5% no recovery

What are some of the potential RFs for ATN-associated mortality?

→ leading causes of death are lung infections, sepsis, CV disease, bleeding d/o's

- pre-existing renal insufficiency
- male gender
- multi-organ failure
- pre-existing chronic diseases
- elderly patients
- oliguria
- respiratory failure with mechanical ventilation
- acute MI
- CVD/seizures

What measures can be taken to prevent ATN?

- identify high risk patients } hx of ARF, elderly, dehydrated patients, DM
- identify diagnostic & therapeutic nephrotoxicities } coronary angiogram, Abx, etc
- **iv isotonic hydration (eg. pre-angiogram)**
- **use of non-ionic contrast } lower incidence of contrast nephropathy**
- use of CO2 angiography
- increase intervals between contrast administration
- pretreatment with **mucomyst** (600mg po bid for 48hrs) } controversial
- pretreatment with Na Bicarb (3 amps in 1L D5W) } likely no better than hydration

What are the RFs for development of, or increased severity of, contrast nephropathy?

→ defined as impaired renal function within 48hrs of contrast administration

→ listed approximately in order (from proven to theoretical) } } } **"RADD Nephrotoxic CHAMP"**

- **Renal insufficiency (most predictive)**
- **Age >65**
- **DM** } must hold metformin x 48hrs (risk of lactic acidosis if renal failure occurs)
- **Dehydration**
- concurrent **nephrotoxic** drugs (eg ACE inhibitors, cyclosporine, NSAIDs, etc)
- **CHF**
- **HTN**
- **Amount of contrast used (high) or recent contrast use**
- **Multiple myeloma/ hyperuricemia**
- **Proteinuria**

What is the classification of proteinuria?

- 1) glomerular } **most common**
 - } increased filtration of normal plasma proteins due to defect in glomeruli
 - } **albumin** makes up majority of proteinuria
- 2) tubulointerstitial } proximal tubules unable to reabsorb normally filtered proteins
 - } usually increased amounts of **LMW proteins** (smaller than albumin)
- 3) overflow } least common
 - } abN amount of LMW proteins in plasma overwhelm proximal tubular reabsorption
 - } eg Bence Jones proteinuria, myoglobinuria, hemoglobinuria
- 4) functional/physiological } no renal or systemic disease
 - } characteristically intermittent and mild (<1g/day)
 - } **fever, exercise, renal venous HTN (CHF, RVT), emotional stress**
 - } **orthostatic proteinuria** is special form of functional proteinuria seen in healthy young adults
 - proteinuria in upright position

What are the theories to explain exercise-induced hematuria?

- 1) direct trauma to kidney (direct blow)
- 2) indirect trauma to kidney (jostling with jogging)
- 3) non-traumatic renal bleed (hypoxia from decreased renal blood flow)
- 4) bladder trauma (flaccid wall jostling against trigone)
- 5) prostate (cycling)
- 6) urethral (cycling)

CHRONIC RENAL FAILURE

Evaluation

What is the definition of chronic kidney disease?

- **sustained kidney damage >3months resulting in GFR <60 mL/min/1.73 m²**
- phases of progressive renal disease include:
 - 1) decreased renal reserve
 - 2) renal insufficiency
 - 3) renal failure
 - 4) frank uremia
- large changes in GFR result in minimal changes in creatinine when overall renal fxn is good
- small changes in GFR result in large changes in creatinine when overall renal fxn is poor

What are the stages of chronic kidney disease (CHART)?

➔ **National Kidney Foundation 2002**

- stage 1 } kidney damage with N or increased GFR (**≥90 mL/min/1.73 m²**)
→ Dx & treat CKD, treat comorbid conditions, slow progression, reduce CV risks
- stage 2 } kidney damage with mild decrease in GFR (**60–89**)
→ estimate progression
- stage 3 } moderate decrease in GFR (**30–59**)
→ evaluate and treat complications
- stage 4 } severe decrease in GFR (**15–29**)
→ evaluate and treat complications
- stage 5 } kidney failure (**<15 or <10 or dialysis**)
→ RRT

What is the significance of renal mass reduction and CKD?

- renal insult or surgical reduction
- normally ~600,000 nephrons per kidney
- **reduction of renal mass by >50% results in progressive glomerular injury**
 - hyperfiltration nephropathy
 - glomerular hypertrophy
 - systemic HTN
- age at loss of renal mass influences renal response } CKD more common if loss of renal mass occurs at younger age
- } glomerular volume increased 5-6 fold in congenital solitary kidney

What are the mechanisms involved in progressive renal disease?

→ when GFR is $<50\%$ of N, progressive renal disease begins, even without initial insult

- apoptosis triggered by ischemia, toxins, or endogenous mediators of damage
 - presence of lethal factors (eg TNF) or absence of survival factors (eg EGF, IGF)
- apoptosis leads to reduction of nephron mass
- reduced nephron mass results in progressive renal injury
 - involves sympathetic activation, renal structural changes & altered gene expression/regulation
 - may involve podocytes
 - ongoing injury due to neurogenic factors, systemic HTN, and hyperfiltration injury
- ultimately results in **glomerulosclerosis & interstitial fibrosis**

What glomerular structural changes are seen with progressive renal disease?

- increased ECM production
 - glomerular hypertrophy (size)
 - glomerular proliferation (#)
 - glomerular BM changes
- \
- leads to glomerulosclerosis and
interstitial fibrosis**

What is the role of family history of ESRD?

- better predictor of future risk of renal failure than BP or blood sugar
- genetics contribute to structural & functional adaptations to a reduction in renal mass
- familial clustering of ESRD reported with DM, HTN, SLE, and HIV-associated nephropathy

What are the causes of CKD/ESRD (CHART)?

→ most forms of CKD progress to ESRD over a 2 to 10yr time course

- 1) **DM (~50%)**
- 2) **HTN (~27%)**
- 3) **GN (~10%)** } **most common outside of N. America**
- 4) interstitial nephritis/pyelonephritis (4.2%)
- 5) miscellaneous (4%) } sickle cell disease, AIDS, trauma, hepato-renal syndrome, etc
- 6) unknown (4%)
- 7) hereditary/congenital cystic disease (3.2%)
- 8) secondary GN/vasculitis (2.2%)
- 9) cancer/tumour (2%)

What are the most common causes of ESRD in young patients (<40yrs)?

- 1) **FSGS**
- 2) **SLE**
- 3) congenital abnormalities of GU tract
- 4) membranous GN

Which primary parenchymal renal diseases have the greatest risk of progression to ESRD?

- 1) FSGS (especially malignant FSGS)
- 2) rapidly progressive GN
- 3) chronic glomerulonephritis
- 4) MPGN (especially type 2 – more sclerotic glomeruli, crescents, interstitial fibrosis)
 - IgA nephropathy progresses to ESRD in only 40% after ~20yrs of disease
 - minimal change disease rarely progresses, especially in kids

What is IgA nephropathy?

- aka Berger's disease
- common cause of GN } **M >> F**
- **progressive renal failure seen in only 40%**
- associated with recent viral illness } gross hematuria present during acute infection
 - } get **recurrent gross hematuria**

What are the poor prognostic features of IgA nephropathy?

- renal impairment
- M gender
- HTN
- proteinuria >2g/day

What are the causes of progressive CKD (CHART)?

→ systemic diseases

- DM
- HTN
- SLE
- Henoch-Schonlein purpura
- systemic sclerosis
- infectious GN
- dysproteinemias/amyloidosis/cryoglobulinemia
- thrombotic microangiopathies
- vasculitis } crescentic GN, acute diffuse GN, ANCA GN, Wegener's granulomatosis, Goodpasture's syndrome, Churg-Strauss syndrome

→ Primary Renal Disease

- idiopathic GN
- **FSGS**
- **RPGN**
- **membranoproliferative GN**
- IgA nephropathy
- minimal change disease

→ tubulointerstitial

- hematologic } sickle cell disease, lymphoproliferative disease, neoplastic
- urologic } stones, UPJO, VUR, PUVs, prune-belly, BPH
- vascular } radiation, HTN, atheroemboli
- metabolic } cystinosis, oxalosis, uric acid nephropathy, hyperCa
- immunologic } renal Tx rejection, Sjogren's syndrome
- toxic } NSAIDs, analgesic, chemo
- immunosuppression } tacrolimus, cyclosporine
- heavy metals } lead, Li

→ Hereditary

- sickle cell
- AD PCKD
- medullary cystic disease
- Alport's syndrome (80% X-linked, 15% AR inheritance, 5% AD inheritance)

What other features are associated with AD PCKD?

→ **most common hereditary renal disease leading to ESRD**

→ only ~50% progress to ESRD

→ PKD1 gene on chromosome 16 and PKD2 gene on chromosome 4

→ "Be DA Real MVP with 8 aCysts"

- Berry aneurysms
- Diverticular disease
- Aortic arch aneurysms
- Renal artery aneurysms
- MV prolapse
- cysts in kidney, liver, pancreas, spleen, lung, pineal gland, arachnoid, SVs

What are the RFs for progression of AD PCKD to ESRD?

- male
- young at presentation
- HTN
- black
- PKD1 gene
- gross hematuria

What factors are associated with ARF in patients with CKD (CHART)?

- nephrotoxic
 - contrast agents
 - ABx (eg aminoglycosides)
 - NSAIDs
 - COX-2 inhibitors
 - chemo agents (cisplatin)
 - anti-rejection meds (cyclosporine, tacrolimus)
- autoregulatory dysfunction
 - ACE inhibitors
 - ARBs
- anatomic/structural
 - AD PCKD + ACE inhibitors
 - obstruction
 - progressive RAS
 - renal vein thrombosis
 - stones
- hemodynamic/perfusion disorders
 - CHF
 - peri-op hypoTN
 - dehydration
 - excessive diuresis
 - sepsis with vasodilation
- parenchymal injury
 - acute MI
 - valvular dysfunction
 - superimposed “new” GN
- interstitial
 - hyperCa
 - hyperuricosuria
 - atheroemboli
- drug-induced
 - cephalosporins
 - sulfa
 - diuretics
 - cimetidine
 - dilantin

What are the RFs for progression from CKD to ESRD?

- HTN
- microalbuminuria/proteinuria
- poor DM control
- smoking
- high dietary protein
- hyperlipidemia
- advanced age

List some of the chemical abN’ities found with CRF.

- hyperK
- metabolic acidosis (kidneys can’t make NH_4 to get rid of excess H^+)
- hypoalbuminemia (proteinuria)
- functionally abN platelets (uremia)
- secondary hyperPTH’ism (from hyper PO_4 , hypoCa, and low Vit D levels)
- hypoCa (decreased GI absorption due to low Vit D levels)
- hyper PO_4 (kidneys can’t excrete PO_4)
- osteomalacia (from Vit D deficiency & aluminum accumulation)

Management

What are the goals of assessing and treating CKD?

- 1) assessment of GFR (function)
 - serum creatinine
 - Cockcroft-Gault
 - eGFR
 - MDRD equation
- 2) level of proteinuria
 - sensitive marker of CKD
- 3) assessment of comorbidities
- 4) limiting factors that contribute to progression & complications
 - if creatinine >2 mg/dL (170 μmol/L), should consider alternatives to contrast imaging and use prophylactic preventative measures

➔ **NIH recommends referral to nephro when creatinine is 1.5 mg/dL (130 μmol/L) in F and 2.0 mg/dL (170 μmol/L) in M**

What are the indications for renal Bx in the setting of CKD?

- GFR <60 mL/min/1.73 m² + abN urinalysis

List therapeutic measures used to prevent the progression of CKD (CHART)

- lifestyle changes } stop smoking, exercise, weight loss
- BP control } <130/80 (if proteinuria >1g/day then aim for <125/75)
- glycemic control } HgA1C <7%
- reduction of proteinuria } ACE inhibitors (altace) significantly slow progression
 - ➔ goal is <0.5 g/day
 - ➔ **combined ACEI + ARBs even better**
- mild protein restriction } 0.6 to 0.8 g/kg/day
- lipid control } HMG-CoA reductase inhibitors also reduce renal cellular damage
- avoidance of nephrotoxic agents
- early referral to nephro
- correction of anemia (keep Hg .12 g/dL or higher)
- optimization of Ca-PO₄ product
- correction of acidosis
- maintenance of fluid balance

What are the complications of ESRD?

- cardiovascular disease } 60% with CRF die of CV disease before dialysis
- HTN
- infections
- neuropathy
- anemia
- malnutrition
- bone disease
- altered QOL

What anti-HTNsive medications are recommended to manage HTN in the setting of CKD?

- **ACEI or ARB + diuretic**
- add CCB if BP >160/100
- add β-blocker if still HTNsive
- if still HTNsive, perform w/u for secondary causes } add minoxidil if w/u negative

RRT

What are the different forms of RRT used for ESRD patients?

- PD } preservation of residual renal function and BP control better than HD
 } weight gain and inadequate long-term dialysis more common with PD
 } **if younger non-DM, survival better if started on PD**
- HD } most common
 } ventricular arrhythmias more common with HD
 } **if older patient with DM, survival better with HD (months)**
- renal Tx } best overall treatment
 } sepsis-associated mortality is 15-fold lower than HD patients
 } → still 20x higher than general population
 } patients on HD for >10yrs have poorer outcomes after renal Tx

What is the life expectancy of patients on dialysis?

- women worse than men for almost all outcomes
- 25% that of general population
- life expectancy of transplant recipient is 2x that of a pt on dialysis
- life expectancy of transplant recipient is only 50-70% that of general population

List indications to change to PD (CHART)?

- access failure
- hypercoagulability
- recurrent CHF
- poor tolerance of HD (intradialysis hypoTN)
- malnutrition
- nursing home care

List indications to change to HD (CHART)?

- repeated catheter malfunctions
- recurrent peritonitis
- UF failure
- hospitalization
- uncontrolled DM
- hypoTN
- psychological burnout
- failure of ADLs

What are the criteria for starting RRT in hospitalized patients? } “AA OK ON PUMP”

- Anuria (< 50cc/12h)
- Azotemia (BUN > 30)
- volume Overload } organ edema (eg pulmonary)
- hyperK (> 6.5)
- Oliguria (< 200cc/12h)
- Na abN’ities (Na > 160 or < 115)
- uremic Pericarditis
- Uremic symptoms } neuropathy, encephalopathy
- severe Metabolic acidemia (pH < 7.1)
- Poisons that are dialyzable

What are the predictors of hospitalization (# per yr) in patients on chronic HD?

→ **CKD patients are 10x more likely to be hospitalized than general population**

→ **length of stay is longer too**

- low albumin
- decreased activity level
- DM as cause of ESRD
- PVD
- white race
- older age
- CHF

What are the most common causes of death in patients with ESRD?

- 1) **cardiovascular disease**
- 2) infection/sepsis

What are the different modalities of HD (CHART)?

- 1) HD
 - convective-based process across semi permeable membrane
- 2) hemofiltration (HF)
 - convective-based solute removal
 - plasma water filtered across highly permeable membrane
 - **more cardiovascular stability**
 - **better removal of HMW metabolites (?sepsis → removal of bad cytokines)**
- 3) hemodiafiltration
 - convective + diffusive process across semi-permeable membrane
 - increased small and large molecule removal (?sepsis → removal of bad cytokines)
- 4) ultrafiltration (UF)
 - plasma water removal
 - fluid removal
- 5) sustained low efficiency dialysis (SLED)
 - slow, convective-based process across semi-permeable membrane
 - **more cardiovascular stability**
 - more efficient clearance of small solutes

What are the components of an optimal disease management program for pts w/ ESRD?

- Interventions that delay progression
 - lifestyle changes } stop smoking, exercise, weight loss
 - BP control } <130/80 (if proteinuria >1g/day then aim for <125/75)
 - glycemic control } HgA1C <7%
 - reduction of proteinuria } ACE inhibitors (altace) significantly slow progression
 - goal is <0.5 g/day
 - **combined ACEI + ARBs even better**
 - mild protein restriction } 0.6 to 0.8 g/kg/day
 - lipid control } HMG-CoA reductase inhibitors also reduce renal cellular damage
 - avoidance of nephrotoxic agents
 - early referral to nephro
- Prevention of uremic complications
 - correction of anemia (keep Hg .12 g/dL)
 - optimization of Ca-PO₄ product (osteodystrophy)
 - correction of acidosis
 - maintenance of fluid balance (edema)
- Modification of morbidity
 - DM control
 - treat PVD
 - treat CAD
 - treat pulmonary disease
- Preparation for RRT
 - renal disease education
 - modality selection
 - timely access placement
 - timely dialysis initiation

Chapter #42 – Urinary Lithiasis: Etiology, Epidemiology, and Pathogenesis

EPIDEMIOLOGY OF RENAL CALCULI

How common are stones?

- lifetime prevalence is 1-15% } 25% have +ve family hx
- recurrence rate without Rx } 10% at 1yr, 35% at 5yrs, 50% at 10yrs

What are the epidemiologic RFs for stone formation?

- 1) gender → 2-3x more common in **men** } estrogen may have protective effect
→ increasing incidence in women
- 2) race/ethnicity → most common in **whites**, least in asians and blacks
→ male preponderance seen mostly in whites, less so in blacks/hispanics
- 3) age → peak incidence during **30's to 50's**
→ uncommon before age 20
- 4) geography → more common in **hotter regions**
→ also more common in **certain regions (?genetics/diet)**
- US, UK, Scandinavia, Mediterranean, northern India, northern Australia
- 5) climate → more common in **hotter, sunnier climates**
→ the effect of dehydration and vitamin D from sun
- 6) occupation → jobs with **heat exposure and dehydration**
→ more common in people with **sedentary jobs**
- 7) socio-economic status → more common among the **affluent** } more dietary indulgences
- 8) BMI and weight → more common in those with **high BMI** } especially in women
- 9) water intake → higher incidence with **decreased water intake**
→ ? higher incidence among those with a “soft water” supply

PHYSIOCHEMISTRY

State of Saturation

What is K_{sp}?

- **solubility product** } the concentration product at the point of saturation
- crystals don't form and existing stones may dissolve if concentration product is <K_{sp}
- crystallization may not occur at K_{sp} due to the presence of inhibitors and other molecules

What is K_f?

- **formation product** } the concentration product at point of crystallization
- crystallization occurs when concentration product of a salt is >K_f } due to supersaturation

What is the metastable zone?

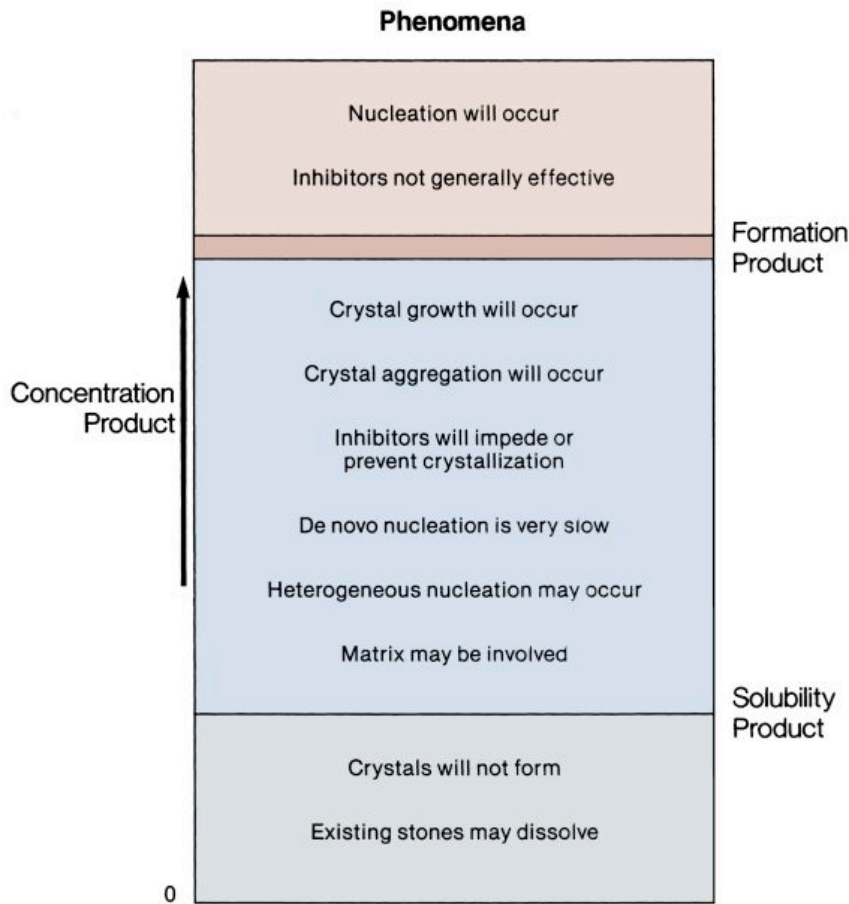
- **concentration product of a salt between K_{sp} and K_f**
→ conditions of solution & inhibitors account for difference between K_{sp} and K_f
- **no spontaneous/homogeneous nucleation or precipitation occurs despite supersaturated urine**
→ crystal formation can occur if there is urine stasis/obstruction or by heterogeneous nucleation (eg on existing stone)

What is the “relative saturation ratio”?

- $\frac{\text{concentration product of urine}}{K_{sp} \text{ of specified stone-forming salt}}$
- the higher the ratio, the more likely the crystallization/precipitation of the salt

What are the 3 major states of urine saturation?

- 1) undersaturated ($<K_{sp}$)
- 2) metastable
- 3) unstable ($>K_f$)



Nucleation and Crystal Growth, Aggregation, and Retention

What is “homogeneous nucleation”?

- **de novo formation of stone nucleus } only occurs $>K_f$**
- nuclei are the earliest crystal structures that WON’T dissolve
- if transit time through nephron is slow enough and supersaturation level is adequate, nuclei will persist and grow (“free crystal particle growth”)
- inhibitors (eg citrate) destabilize nuclei while promoters stabilize nuclei
- if enough nuclei form and grow, they will aggregate to form a stone

What is “heterogeneous nucleation”?

- microscopic impurities or other urine constituents (**epithelial cells, cell debris, casts, RBCs, other crystals**) can facilitate nucleation by adsorption of the crystal components
- requires less energy than homogeneous nucleation } **can occur if $>K_{sp}$**

What is the role of papillary plaques (Randall's plaques) in stone formation?

- **much more common in stone formers } 75% vs 40%**
 - **urine is most supersaturated in the renal papilla**
 - correlates with Ca levels in urine and # of stone related episodes } "fixed particle growth"
- 1) Stoller et al → injury to vasa recta near renal papilla
 - repair of wall involves atherosclerotic-like reaction leading to calcification
 - calcification erodes into collecting duct where it serves as a nidus for stones
 - 2) Evan et al → Ca apatite (PO₄) plaques originate in BM of thin loops of Henle
 - plaque extends through interstitium to subepithelial location
 - once they erode through urothelium, they act as a nidus for stone nucleus

Inhibitors and Promoters of Crystal Formation

What are some known urinary stone inhibitors? } } } "GAG MI CUNT BRO"

- **no known inhibitors that affect uric acid crystallization**
- **GAG** (can occasionally act as promoter of crystal nucleation)
- **Acid mucopolysaccharides**
- **Glucosamine**
- **Magnesium**
- **Inorganic pyrophosphate**
- **Citrate } most potent complexor of Ca**
- **Urinary prothrombin fragment 1 } most potent inhibitor in normal urine**
- **Nephrocalcin glycoprotein (made in PCT & TAL)**
- **Tamm-Horsfall glycoprotein (made in TAL & DCT) } most abundant protein in urine & most potent stone aggregation inhibitor**
- **Bikunin** (protein made in liver)
- **RNA fragments**
- **Osteopontin/uropontin** (made in TAL & DCT)

How do urinary stone inhibitors work?

- 1) inhibits nucleation
 - citrate } binds to Ca
 - nephrocalcin } inhibits COM stones
 - uropontin/osteopontin } inhibits Ca oxalate stones
 - bikunin } inhibits Ca oxalate stones
- 2) inhibits growth
 - citrate } inhibits growth of only Ca PO₄ stones
 - nephrocalcin } COM stones
 - uropontin } Ca oxalate
 - bikunin } Ca oxalate
- 3) inhibits aggregation
 - citrate } binds to Ca
 - **Mg** } binds to oxalate
 - nephrocalcin } COM stones
 - **Tamm-Horsfall protein** } inhibits COM stones → doesn't affect nucleation/growth
 - uropontin } Ca oxalate
 - bikunin } Ca oxalate

Matrix

What is stone matrix?

- the non-crystalline portion of stone
- usually accounts for ~2.5% of total weight of stone
 - pure matrix stone } can account for up to 65% of stone, when associated with UTIs
- composed of up to **65% glycoprotein**, 10% non-amino sugars, 10% bound water, 12% organic ash, and 5% glucosamine
- *E. coli* may increase matrix formation
- **substance A** is a component of matrix in all stone formers and is immunogenically unique

- only 6-15% of dietary oxalate is absorbed
→ **equally in small bowel & colon**
- forms complex with Ca/Mg which limits gut absorption
- *Oxalobacter formigenes* uses oxalate as energy source, thereby reducing absorption
- **most of oxalate made in liver**
→ renal excretion (glomerular filtration + PCT secretion)
→ **pre-cursors of oxalate are glyoxylate & ascorbic acid (Vit C)**
- **absorbed oxalate is nearly completely excreted in PCT of kidney**

CALCIUM STONES (75%)

What is the definition of HYPERCALCIURIA?

- >**200mg** of urinary Ca per day after adherence to a 400mg Ca and 100mg Na diet for 1 week
- excretion of >4mg/kg/day
- **most common abnormality found in Ca stone formers**
- **high Na diet can increase calciuria**

What are the causes of hypercalciuria?

- 1) absorptive hypercalciuria
 - increased Ca excretion after oral Ca load
 - **N fasting urinary Ca (most cases) + N serum Ca + N or suppressed PTH**
 - possibly related to Vit D receptor upregulation
 - type 1 } hypercalciuria despite low Ca diet (severe & less common)
 - type 2 } normal Ca excretion on restricted Ca diet
- 2) renal leak hypercalciuria
 - impaired PCT reabsorption of Ca
 - leads to secondary hyperPTH'ism
 - **↑ fasting urinary Ca + N serum Ca + ↑ PTH + ↑ Vit D**
 - possibly related to Na intake, PGs, genetic abnormalities (Dent's, Bartter's)
- 3) resorptive hypercalciuria (uncommon)
 - **usually associated with primary hyperPTH'ism**
 - **↑ urinary Ca + hyperCa + ↑ PTH + ↑ Vit D**
 - high PTH results in ↑'d gut absorption (Vit D) & ↑'d bone resorption
 - hyperCa present in most cases, BUT can rarely be N
 - if N serum Ca, then resembles renal leak
 - if truly resorptive, serum Ca will worsen after "thiazide challenge"
 - also get elevated urinary PO₄ and cAMP levels found
 - can also be due to malignancy (↑ PTH), sarcoid (↑ Vit D), TB, hyperT₄, pho, etc
- 4) primary idiopathic hypercalciuria (most common cause of Ca stones in kids)

What is Dent's disease?

- X-linked recessive stone disease (Xp11) } mutation affects CL channel in thick AL (CLC-5)
- **microhematuria + LMW proteinuria + hypercalciuria**
- **CRF + stones + nephrocalcinosis** (medullary)

What are the features of Bartter's syndrome?

- AR genetic defect involving thick AL of kidney } get **hypoK, hypoCL, metabolic alkalosis**
 - can affect Na-K-Cl gene, K channel gene, Cl channel gene
- results in **hypercalciuria + stones**

What are the causes of hyperCa, hypercalciuric stones (resorptive)?

- 1) **PTH-dependent (elevated PTH)**
 - **usually primary hyperPTH (most common cause of outpatient hyperCa)**
 - malignancy } breast or lung (60%), RCC (10-15%), head & neck (10%), lymphoma/MM (10%)
 - } from direct bone destruction AND production of **PTH-like polypeptide**
 - also due to TGF- α , IL-1, TNF (activates osteoclasts)
 - } **most common cause of inpatient hyperCa**
 - familial hypocalciuric hyperCa
- 2) **PTH-independent**
 - sarcoidosis (↑'d Vit D production)
 - steroids (↑'d bone resorption)
 - immobilization
 - TB
 - Vit A toxicity & Vit D toxicity
 - thiazides
 - thyrotoxicosis
 - milk-alkali
 - pheochromocytoma
 - leprosy
 - Cushing's
 - AIDs
 - theophylline
 - coccidiomycosis

Table 42-3 -- Hypercalcemic States

Condition	Parathyroid Hormone	Phosphorus	Urine Calcium	Glomerular Filtration Rate	Other
Thiazide	N	N	L	N	Low K+
Malignant tumors	NLH	L/N	H	N/L	Osteolytic or sclerotic bone lesions
Vitamin D excess	L	N/H	H	N/L	
Sarcoidosis	L	N	H	N/L	High 1,25(OH)2D3
Coccidioidomycosis	L	N	H	N/L	High 1,25(OH)2D3
Silicosis	L	N	H	N/L	High 1,25(OH)2D3
Plasma cell granuloma	N	N	—	L	High 1,25(OH)2D3
Leprosy	N	N	H	L	High 1,25(OH)2D3
Hypothyroidism	N	N	H	N	High 1,25(OH)2D3
Primary increase in 1,25(OH)2D3	L	N	H	N	High 1,25(OH)2D3
Pheochromocytoma	L/N	N	H	N	High 1,25(OH)2D3
Hyperthyroidism	N	N	L/N	N	High calcitonin has been reported
Tuberculosis	L	H	H	L	
Addison's disease	N	N	L/N	N	
Familial hypocalciuric hypercalcemia	H	N	N	N	
Lithium	N	—	—	—	Asymptomatic
Theophylline	L	N	H	N	
Paget's disease	L	N	H	N	
Immobilization	L	L/N	—	—	
Acquired immunodeficiency syndrome					Usually only hypercalciuric Low 1,25(OH)2D3

From Coe FL, Park JH (eds): *Nephrolithiasis: Pathogenesis and Treatment*. Chicago, Year Book Medical Publishers, 1988, p 85.

H, high; L, low; N, normal; 1,25(OH)2D3, 1,25-dihydroxyvitamin D3.

What are the GU manifestations of sarcoidosis? (AUA Update #14 – 2008)

→ “GU SARC Has Pulmonary Nodal Disease”

- 1) Genital skin lesions (scrotal, penile)
 - diffuse granulomatous inflammation OR discrete nodules
- 2) Urolithiasis (calcium) → 10%
 - can be 1st sign of sarcoidosis
 - hyperCa (10-20%), hypercalciuria (60%) } activated macrophages upregulate 1 α -hydroxylase resulting in excess 1,25-Vit D (calcitriol)
Rx → steroids down-regulate 1 α -hydroxylase
- 3) Scrotal mass (testis, epididymis)
 - testis mass can be mistaken for Ca
- 4) Azoospermia (obstructive)
- 5) RPF
- 6) Chronic renal failure (uncommon)
 - granulomatous interstitial nephritis (GIN)
- 7) Hematuria
- 8) Pseudotumours (rare)
 - can resemble renal lymphoma
 - if lung nodules, can resemble metastatic RCC
- 9) Nephrocalcinosis (medullary) → <5%
- 10) Destrusor areflexia, DSD
 - from thoracic spinal cord involvement
 - extremely rare but can get bladder lesions } resembles malacoplakia BUT has **asteroid bodies**

\ renal mass in sarcoidosis is
/ more likely to be RCC

What is the definition of HYPOCITRATURIA?

- urinary citrate <320mg/day
- metabolic acidosis ↓'s urinary citrate } ↑'d renal reabsorption + ↓'d synthesis by peritubular cells

What are the causes of hypocitraturia?

→ **systemic acidosis is primary determinant of urinary citrate excretion**

- 1) distal RTA } inability to acidify urine after oral acid load (NH₄Cl)
 } high urine pH (>6.8) + hyperCL + hypoK + low serum HCO₃ (met acidosis)
- 2) diarrheal states } intestinal alkali loss results in systemic acidosis
- 3) thiazide-induced } induced hypoK + intracellular acidosis
- 4) high-protein diet } acid load
- 5) idiopathic (un-related to acidotic state)

List causes of hypocitraturia. }}} "HARD TIP"

- HypoK
- Acidosis
- RTA (distal)
- Diarrheal states
- Thiazides
- Idiopathic
- Protein-rich diet

List factors that increase urinary citrate levels?

- 1) alkalotic states
- 2) elevated PTH
- 3) estrogen
- 4) growth hormone
- 5) Vit D

What is RTA?

- **family of syndromes due to defects in renal tubular H⁺ secretion & urinary acidification**

- RTA type 1 } aka "classic RTA" or "distal RTA" (most common form)
 } **adults (2/3)** present with stones, whereas kids (1/3) present with FTT, vomiting, diarrhea
 } **defective H⁺ ATPase in collecting duct (intercalated cells)**
 → failure of H⁺ secretion in distal nephron even after NH₄ chloride load test
 } acquired ("POST CLAAASHH") VS idiopathic VS congenital (uncommon - AD & AR)
 } **hyperCL + hypoK + NAG met. acidosis + high urine pH (>5.5) despite low serum HCO₃**
 } **hypocitraturia + hypercalciuria + hyperphosphaturia**
 → 70% get **Ca PO₄ STONES** (brushite) & **nephrocalcinosis** (medullary)
 } acidosis leads to secondary hyperPTHism from **hypoCa**
 → get metabolic bone disease
 Rx → K citrate or NaHCO₃
- RTA type 2 } aka "proximal RTA"
 } more common in **kids** (can get osteomalacia & growth retardation)
 } **defective HCO₃ reabsorption in PCT**
 → loss of HCO₃ in urine + overwhelming of distal H⁺ secretion
 } sporadic (more common) VS congenital (less common)
 } **acidemia usually less severe** than type 1
 - DCT can still secrete H⁺ to try to offset HCO₃ loss
 } **hyperCL + hypoK + NAG met. acidosis + N/low urine pH (slightly <5.5)**
 + **mildly low serum HCO₃ (15-20mEq/L)**
 } **N urine citrate levels (NO stones)**
 } often part of Fanconi's syndrome
 → leak of phosphate, glycogen, amino acids, uric acid, protein
 } can also develop growth retardation & metabolic bone disease (more common than dRTA)
 Rx → NaHCO₃ + K supplementation
- RTA type 3 } considered variant of type 1 (distal + proximal issue)
- RTA type 4 } **impaired secretion of H⁺ and K⁺ in DCT**
 } associated with **HTN & CRF (DM, interstitial renal disease)**
 → often also associated with aldosterone deficiency or resistance
 } **hyperCL + hyperK + NAG met. acidosis + low urine pH (<5.5)**
 } NO stones (reduced renal excretion of stone-forming substances due to CRF)
 Rx → mainly directed at controlling hyperK
 → treat aldosterone deficiency (fludrocortisone)

Which patients should be evaluated for RTA? } } } “ACID Paint BRUSH”

- Azotemia
- **CaPO₄** stones
- Infants with FTT
- Decreased K
- Pyelonephritis (chronic)
- Bilateral stones
- Recurrent stone formers (>2/yr)
- Unexplained metabolic acidosis (NAG)
- Sponge kidney } MSK, medullary nephrocalcinosis
- Hypocitraturia

List features used to differentiate type 1 RTA from type 2 RTA.

	Type 1 RTA	Type 2 RTA
1) hypocitraturia	present (stones)	absent (no stones)
2) urine pH	>5.5	N/low urine pH
3) serum HCO ₃	low	mildly low (15-20)
4) age group	more common in adults	more common in kids

List the causes of acquired distal RTA. } } } “POST CLAAASHH”

- Cirrhosis
- Lithium
- Analgesic nephropathy
- ATN
- Autoimmune disease } thyroiditis, SLE, Sjogren’s
- Sarcoidosis
- HyperPTH’ism
- Hypercalciuria (familial)
- Pyelo (chronic)
- Obstruction
- Sick cell anemia
- Transplant (renal)

List ways that citrate can decrease Ca stone formation. } } } “Complex SNAG Protein”

- 1) most potent Ca **Complexor**
- 2) inhibits **Sedimentation** of Ca oxalate crystals
- 3) directly prevents spontaneous **Nucleation** of Ca oxalate
- 4) inhibits **Agglomeration** of Ca oxalate crystals
- 5) prevents **Growth** of Ca oxalate & Ca PO₄ crystals
- 4) enhances inhibitory effects of Tamm-Horsfall **protein**

What is the definition of HYPERURICOSURIA?

- urinary uric acid >**600mg/day** } mostly male
- **↑’d urinary Na-urate** } promotes Ca oxalate stones at pH >5.5 → heterogeneous nucleation
→ **uric acid reduces effectiveness of stone inhibitors (eg GAG)**

What are the causes of hyperuricosuria?

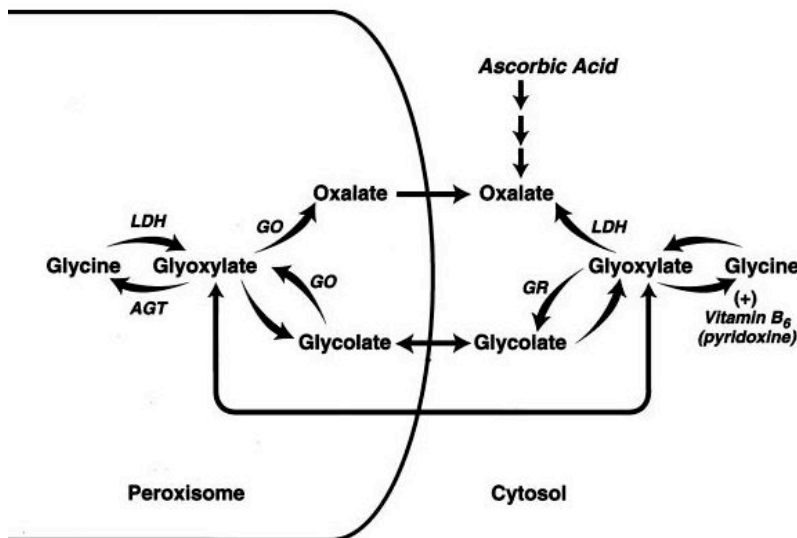
- 1) dietary excess of purines (most common cause)
 - 2) uric acid overproduction } gout, myeloproliferative & lymphoproliferative d/o’s, hemolytic d/o’s, multiple myeloma, hemoglobinopathies and thalassemia
- stone formers w/ hyperuricosuria have ↑’d rates of stone formation & more severe symptoms

What is the definition of HYPEROXALURIA?

- urinary oxalate **>40mg/day** } glycine and ascorbic acid are precursors to oxalate
- ↑'d oxalate complexes with Ca and forms Ca oxalate stones
- ↑'d oxalate may also lead to increased crystallization due to tubular cell injury + free radical formation

What are the causes of hyperoxaluria?

- 1) primary oxalosis
 - rare **AR disorder** that prevents conversion of glyoxylate to glycine
 - glyoxylate gets converted in liver to oxalate instead } **get >100mg/day of oxalate**
 - aggressive stone formation, nephrocalcinosis
 - type 1 = **lack of AGT** enzyme (liver)
 - type 2 = lack of glyoxylate reductase (liver) } less aggressive course wrt renal failure
 - get **CORTICAL nephrocalcinosis**
 - if un-Rx'd (liver-kidney Tx), 50% will have ESRD by age 15 and is assoc'd with ~30% death rate
- 2) enteric (most common acquired cause)
 - chronic diarrheal states (Crohn's, Celiac sprue, short gut, small bowel resection, etc)
 - fat malabsorption results in saponification of FA's with Ca & Mg
 - results in **↑'d oxalate available for absorption** d.t. ↓'d Ca/Mg complexing
 - malabsorbed FA's & bile salts cause **↑'d oxalate absorption in colon too**
 - also get **dehydration, hypoK, hypomagnesuria, hypocitraturia, acidic urine**
- 3) dietary
 - ↑'d oxalate-rich diet (nuts, chocolate, spinach, broccoli, strawberries, rhubarb, brewed tea)
 - ↑'d Vit C diet
 - may be due to **absence of Oxalobacter formigenes** (oxalate-degrading bacterium)
- 4) idiopathic



→ OXALATE METABOLISM PATHWAY

What is the definition of HYPOMAGNESURIA?

- urinary Mg **<40mg/day**
- rare cause of Ca stones } Mg normally complexes with oxalate and Ca
- associated with low citrate levels

What are the causes of hypomagnesuria?

- 1) poor dietary intake
- 2) reduced intestinal absorption } diarrheal states (IBD, etc)

URIC ACID STONES (7%)

What is uricase?

- enzyme that catalyzes the conversion of uric acid to allantoin \ **humans & dalmations**
- allantoin is 10-100 times more soluble in urine than uric acid / **lack uricase**

What is the importance of urine pH in uric acid stone formation?

- **urine pH is the critical factor in determining uric acid solubility**
- **most patients with uric acid stones have acidic urine + N urinary uric acid levels**
- at pH <5.5, even low concentrations of uric acid are >Kf
- at pH >6.5, even concentrations of uric acid >1200mg/L remain soluble (<Kf)
- patients with acidic urine **can also form Ca oxalate stones** } heterogeneous nucleation

What are the common findings of patients with uric acid stones?

- urine pH <5.5 (pKa)
- radiolucent stones
- hyperuricemia
- tend to make lots of small stones ... orange in colour on endoscopy
- produce small amounts of cyanide on laser lithotripsy

What metabolic defects are seen in pts with gout?

- **20% with gout have uric acid stones**
- impaired renal production of NH_4 } **acidic urine** \ **most with gouty diathesis have**
- overproduction of uric acid } **N urinary levels of uric acid**
- impaired renal uric acid secretion / **BUT with acidic urine**

What ethnic populations have increased uric acid stones?

- Jews & Italians

What are the 3 main determinants of uric acid stone formation?

→ **no known inhibitors of uric acid crystallization**

1) **low urine pH** (ie "gouty diathesis") } **MOST IMPORTANT FACTOR**

→ **most have N urinary uric acid + acidic urine pH**

- associated with insulin resistance & obesity
 - impaired renal production of NH_4 , so more free H^+ is present to acidify urine
- associated with loss of diurnal variation in urinary pH
 - loss of usual alkalization of urine seen in am & post-prandially
- increased animal protein diet
 - acidifies urine, decreases urine citrate & increases urine uric acid

2) **hyperuricosuria**

→ **differs from gouty patients in that they have hyperuricosuria + N urine pH**

- urinary uric acid >600mg/day
- predisposes to uric acid stones AND Ca oxalate stones
 - dietary excess of purines
 - uric acid overproduction } gout, myeloproliferative & lymphoproliferative disorders, multiple myeloma (MM), hemolytic disorders, hemoglobinopathies & thalassemia, etc
- stone formers w/ hyperuricosuria have higher rates of stone formation & more severe symptoms

3) **low urinary volume**

- low urinary volumes increase risk of uric acid supersaturation
 - eg dehydration

What is the DDX of hyperuricemia?

- primary gout
- Lesch-Nyhan disease
- high cell turnover states } myeloproliferative d/o's, chemo, RADs, etc
- sarcoidosis
- CRF
- endocrine dysfunction (eg DM)
- EtOH'ic & starvation ketoacidosis
- meds } ASA, HCTZ, cyclosporine, ethambutol, etc
- ↑'d activity of 5-phosphoribosyl-1-pyrophosphate synthetase

What are the causes of uric acid stones?

- 1) congenital
 - abnormal renal tubular urate transport
 - abnormal uric acid metabolism eg Lesch-Nyhan syndrome
- 2) acquired
 - chronic diarrhea
 - volume depletion
 - myeloproliferative disorders
 - high animal protein diet
 - uricosuric drugs
- 3) idiopathic
 - obesity !!!

What are the RFs for uric acid stone formation? } } "They Make GOLDD'N PeePee"

- 1) **Thalassemia**
- 2) **Myeloproliferative disorders**
- 3) **Gout**
- 4) **Obesity**
- 5) **Lesch-Nyhan syndrome**
- 6) **DM**
- 7) **Dehydration** (diarrhea, colectomy, ileostomy, etc)
- 8) **Neoplastic disease**
- 9) **Purine-rich diet** → red meat
- 10) **Pregnancy**

CYSTINE STONES (1%)

What is cystinuria?

- **AR disorder** characterized by a defect in intestinal & renal PCT transport of dibasic amino acids
→ **cystine, ornithine, lysine, arginine (COLA)**
- high urinary concentrations of each BUT only cystine is poorly soluble (especially in acidic urine)
- rare cause of stones in adults (<1%), more common in kids (~10%)
- **3 types of cystinuria** } type A (chromosome 2 mutation)
 } type B (chromosome 19 mutation)
 } type AB (chromosome 2 & 19 mutations)
 → type B has higher urinary cystine } but SAME RATE OF STONES
- average age at Dx is ~12yrs
- stone episode usually every 2-5 yrs

How do cystine stones form?

- **error of transepithelial transport** involving intestine & kidneys
→ can't reabsorb amino acids (**Cystine, Ornithine, Lysine, Arginine**)
- cystine crystallizes when concentration in urine is >250 mg/L
- usually present at young age with +ve family hx of stones
- often associated with **hypocitraturia, hypercalciuria & hyperuricosuria**

What are the sources of cystine?

- absorbed from gut
- converted from methionine
- reabsorbed from PCT

What are the factors that contribute to cystine crystallization?

- 1) cystine concentration (crystallizes at N urine conditions) } **no inhibitors of cystine stones**
- 2) urine pH → more crystallization at **acidic pH**
- 3) ionic strength → more soluble at higher ionic strength
- 4) urinary macromolecules → presence of macromolecules (eg colloid) increases solubility

List disorders that have been associated with cystinuria } } } “MR MD PHD”

- **M**ental retardation
- **R**etinitis pigmentosa
- **M**uscular hypotonia
- **D**own syndrome (trisomy 21)
- **P**ancreatitis (hereditary)
- **H**emophilia
- **D**MD

STRUVITE STONES (5-15%)

What are struvite stones?

- **Mg NH₄ PO₄ stones** } **may also contain carbonate apatite (CaPO₄CO₃)**
- formed only in association with UTI by **urea-splitting bacteria** } urease-forming bugs
 - most commonly Proteus, Klebsiella, Pseudomonas, corynebacterium and Staph
 - **Proteus mirabilis is most common**
 - E. coli does NOT produce urease BUT can still be associated with stones
- forms in **alkaline urine (pH>7.2)** with NH₃ in urine
- more common in women (2:1)
- can grow rapidly → forming staghorn stones

How do struvite stones usually present?

- weakness, malaise, loss of appetite
- fever
- flank pain
- dysuria
- LUTS +/- hematuria
- XGP
- staghorn stone

What is the most common composition of staghorn stones?

- 1) **struvite** } **67%**
 - 2) cystine
 - 3) uric acid
 - 4) COM
- **isolated CaPO₄ is likely the least common to form staghorn**

What are the RFs for development of struvite stones? } } } “Urine Can OFFEND People”

- **those at risk for infections**
- Urinary diversion
- Congenital urinary tract malformations
- Obstructed urinary tract
- Female (2x more)
- FB in GU tract (eg Foley)
- Elderly
- Neurologic disorders
- **DM**
- **Premature infants**

Which bacterial organisms produce urease?

Table 42-4 -- Organisms That May Produce Urease

Organisms	Usually (>90% of Isolates)	Occasionally (5%-30% of Isolates)
Gram negative	<i>Proteus rettgeri</i>	<i>Klebsiella pneumoniae</i>
	<i>Proteus vulgaris</i>	<i>Klebsiella oxytoca</i>
	<i>Proteus mirabilis</i>	<i>Serratia marcescens</i>
	<i>Proteus morganii</i>	<i>Haemophilus parainfluenzae</i>
	<i>Providencia stuartii</i>	<i>Bordetella bronchiseptica</i>
	<i>Haemophilus influenzae</i>	<i>Aeromonas hydrophila</i>
	<i>Bordetella pertussis</i>	<i>Pseudomonas aeruginosa</i>
	<i>Bacteroides corrodens</i>	<i>Pasteurella</i> species
	<i>Yersinia enterocolitica</i>	
	<i>Brucella</i> species	
Gram positive	<i>Flavobacterium</i> species	<i>Staphylococcus epidermidis</i>
	<i>Staphylococcus aureus</i>	<i>Bacillus</i> species
	<i>Micrococcus</i>	<i>Corynebacterium murium</i>
	<i>Corynebacterium ulcerans</i>	<i>Corynebacterium equi</i>
	<i>Corynebacterium renale</i>	<i>Peptococcus asaccharolyticus</i>
	<i>Corynebacterium ovis</i>	<i>Clostridium tetani</i>
	<i>Corynebacterium hofmannii</i>	<i>Mycobacterium rhodochrous</i> group
Mycoplasma	T-strain <i>Mycoplasma</i>	
	<i>Ureaplasma urealyticum</i>	
Yeasts	<i>Cryptococcus</i>	
	<i>Rhodotorula</i>	
	<i>Sporobolomyces</i>	
	<i>Candida humicola</i>	
	<i>Trichosporon cutaneum</i>	

→ E COLI DOES NOT PRODUCE UREASE !!!

List bacterium that produce urease. }}} "PACK PUSSY"

- **P**roteus
- **A**eruginosa (*Pseudomonas*)
- **C**orynebacterium
- **K**lebsiella
- **P**rovidencia
- **U**reaplasma urealyticum
- **S**taph aureus
- **S**erratia
- **Y**ersinia

Why is *E. coli* frequently associated with stone formation?

→ NOT a urease-splitting organism

- 1) inhibits activity of stone inhibitors such as urokinase & sialidase
- 2) injury to urothelium allows crystal adherence

Miscellaneous Stones

What are Xanthine stones?

- **radiolucent stones**
 - **AR hereditary** disorder of **xanthine oxidase enzyme** that normally converts xanthine to uric acid
→ get build up of xanthine, which is very poorly soluble in urine
 - very high levels of allopurinol, a xanthine oxidase inhibitor, can also lead to xanthine stones
→ eg high dose allopurinol for Lesch-Nyhan syndrome
- Rx → increased water intake

What are 2, 8-dihydroxyadenine stones?

- **radiolucent stones similar to uric acid**
 - **due to AR inherited deficiency in adenine phosphoribosyltransferase (APRT)**
→ can be confused with Lesch-Nyhan syndrome (uric acid stones)
 - 2, 8-DHA stones are very insoluble at any pH
- Rx → allopurinol can prevent stone formation

What are ammonium acid urate stones?

- **radiolucent stones**
- form with **low urine volume, acidic urine pH, low urine Na**

List conditions associated with ammonium acid urate stones

- laxative abuse } low urine Na
- recurrent UTIs
- recurrent uric acid stone formation } low urine volume and acidic pH
- IBD (colectomy + ileostomy) } low urine volume, low urine Na, and acidic urine
- obesity } acidic urine

What are matrix stones?

- **radiolucent stones**
- often confused with tumour or uric acid stones
- by weight, composed of **2/3 mucoprotein and 1/3 mucopolysaccharide**
→ pure matrix stone made of 65% matrix protein
→ usually matrix component of Ca stones represent only ~2.5% of weight
- may be associated with low urine Ca or proteinuria (renal failure patients)

List stones that are radiolucent on KUB. } } } “U Don’t See The Xray IMAGE”

- 1) Uric acid
- 2) 2,8-Dihydroxyadenine
- 3) Silicate
- 4) Triamterene
- 5) Xanthine
- 6) Indinavir → **only known stone to be radiolucent on CT also**
- 7) Matrix
- 8) Ammonium acid urate
- 9) Guaifenesin
- 10) Ephedrine

What are some medication-related stones?

- 1) **meds that directly form stones (ALL RADIOLOGIC)** } } } “Silicates GET SIC”
 - **Silicates** (eg Mg silicate antacids) → stones form w/ consumption of large amounts
 - **Guaifenesin** (expectorant) → metabolite forms stone
 - **Ephedrine** (cold meds, herbal ecstasy, Ma Huang, etc) → metabolite forms stones
 - **Triamterene** (K⁺ sparing diuretic) → usually incorporates onto existing stone/nidus
→ doesn't usually form pure triamterene stone
(triamterene or its sulfate metabolite)
 - **Septra** (TMP-SMX)
 - **Indinavir** (protease inhibitor) → high urinary excretion & poor solubility at N urine pH
→ more soluble at pH <5.5
→ radiolucent even on CT
 - **Cipro**
- 2) **meds that indirectly promote stone formation** } } } “Can PLATE FAST”
 - **Cytotoxic agents** → high cell turnover and increased uric acid stones
 - **PO₄-binding antacids** → hypercalciuria
 - **Laxatives** → persistent diarrhea leads to ammonium acid urate stones
 - **Acetazolamide** (carbonic anhydrase inhibitor) → metabolic acidosis + urinary alkalization,
→ results in hypocitraturia (CaPO₄ stones)
 - **Thiazides** → intracellular acidosis and subsequent hypocitraturia
 - **Excess Vit D** → hypercalciuria
 - **Furosemide** → hypercalciuria
 - **Allopurinol** → high doses can lead to xanthine stones
 - **Steroids** → hypercalciuria
 - **Topiramate** (antiepileptic) → acts like a carbonic anhydrase inhibitor

Anatomic Predisposition to Stones

What anatomic abnormalities predispose to stone formation?

- 1) UPJ obstruction
 - stones found in **20% of patients with UPJO**
 - these patients have similar metabolic risks as other stone formers → NOT just stasis
- 2) Horseshoe kidneys
 - stones found in **20% of patients with horseshoe kidneys**
 - predisposed to UPJO due to high insertion of ureter
 - also have similar metabolic risks as other stone formers → NOT just stasis
- 3) Caliceal diverticula
 - **40% of patients with caliceal diverticula form stones**
 - also have similar metabolic risks as other stone formers → stasis plays bigger role here
- 4) Medullary Sponge Kidney
 - ectasia/dilation of the collecting ducts
 - **get nephrocalcinosis + stones**
 - recurrent UTIs & stasis in tubules increase risk of stone formation
 - many have metabolic risks like other stone formers → **MAINLY hypercalciuria & hypocitraturia**
 - RTA is NOT cause of stones in MSK

List some of the physiologic changes of pregnancy

- ## What is specific about stones in pregnancy?

- **usually pass most stones** → dilated ureters (progesterone effect on smooth muscle)
 - found in 90% off pregnant women
 - persists for 4-6 weeks post-partum
- hydro mainly due to extrinsic compression by gravid uterus → hydro usually worse on R
- U/S is 1st line imaging modality, but can miss up to 40% of stones
- like in non-pregnant women, more common in whites than blacks
- **overall stone risk similar to non-pregnant women → similar stone compositions**
- may be associated with **increased risk of PROM**

- 1) hydronephrosis → stasis
- 2) increased GFR → increased filtered Ca, Na, and uric acid found in urine
- 3) placental production of Vit D → hypercalciuria

→ also get increased excretion of inhibitors such as citrate, Mg, and glycoproteins so overall stone risk is similar to non-pregnant women

Acute Renal Colic

What is the work-up for acute renal colic?

→ History

- nature, onset, duration, location of pain, exacerbating factors, alleviating factors, LUTs, referred pain into groin
- fever, chills } **r/o pyelonephritis**
- hx of stones, type of stone, treatment
- PMHx (esp. stone RFs) } bowel resection, chronic diarrhea, IBD, gout, recurrent UTIs, DM, pregnancy, renal insufficiency, solitary kidney, osteoporosis, etc
- Dietary Hx } fluid intake, red meat, caffeine, tea,
- Meds } triamterene, calcium, Vit D, acetazolamide, Mg antacids, ephedrine, indinavir, etc
} ASA, coumadin
- EtOH, smoking, drugs

→ Physical

- VS's
- abdo } peritoneal signs, CVA tenderness, abdo masses
- GU exam } r/o primary testicular/labial pathology

→ Lab tests

- CBC, lytes, BUN, creatinine, LFTs, Ca } mild leukocytosis common but rarely >15 unless patient had infection
- β HCG if applicable
- urinalysis } normal urinalysis seen in up to 20%

→ Imaging

- non-contrast CT
- KUB
- U/S is first line if pregnant } hydroureteronephrosis to level of pelvic brim may be physiologic
} RI >0.7 highly suggestive of obstruction

What are the CT findings suggestive of a ureteral stone?

- hydroureteronephrosis
- periureteral stranding
- UVJ edema

What are the management principles of acute renal colic?

- 1) r/o pyelonephritis } temp, CBC, urinalysis
→ urgent decompression required
- 2) pain control
→ NSAIDs (better than opioids)
→ opioids
→ multi-modal pain control best
- 3) fluids
→ **increased hydration DOES NOT reduce pain or need for intervention (2 RCTs)**
→ maintenance fluids sufficient
- 4) admission criteria
→ associated pyelonephritis
→ solitary kidney
→ bilateral stones
→ intractable pain or N/V
→ failure of conservative therapy (multiple ER visits with renal colic)
→ significant co-morbidities (renal failure, DM, etc)
- 5) medical expulsion therapy
→ CCB
→ α -blockers (eg flomax)
- 6) follow-up
→ repeat imaging at follow up to assess passage of stone (functional test – eg lasix renal scan)

List hereditary disorders associated with stones?

- 1) AD
 - **D**istal RTA
- 2) AR
 - **C**ystinuria
 - primary hyperoxaluria (**O**xalosis)
 - **A**denine (2,8-DHA)
 - **X**anthinuria
 - **B**artter's syndrome
- 3) X-linked
 - **XR** nephrolithiasis syndrome
 - **L**esch-Nyhan (uric acid stones)
 - **H**yphosphatemic Rickets syndrome
 - **D**ent's disease (Ca stones) } mutation in Cl- channel in TAL
 } LMW proteinuria, hypercalciuria, microhematuria

- 1) related to renal failure } hypercalciuria → renal tubular dysfunction
 - } hyperoxaluria
 - } dehydration
 - } iatrogenic → Ca supplements
 - } hyperCa → secondary hyperPTH
- 2) related to Tx } foreign bodies → suture
 - } UVJ strictures
 - } steroid use

- 1) local factors → **chronic UTIs** (urea-splitting bacteria)
→ **mucus and FBs** (eg staples)
→ urine stasis
- 2) systemic → dehydration
→ acidosis
- 3) lack of urinary inhibitors → acidosis leads to **hypocitraturia**
→ hypoMg
- 4) lithogenic metabolic defects → hypercalciuria
→ hyperoxaluria (from fat malabsorption)
→ decreased urine pH

→ get Ca oxalate stones

- 1) hyperoxaluria
- 2) hypocitraturia

- **Dehydration**
- **Underweight at birth**
- **TPN**
- **Theophylline**
- **Cystinuria**
- **HyperPTH'ism (congenital)**
- **Steroids**
- **RTA (distal)**
- **Lasix**
- **Sepsis**

What are the causes of stones in children?

→ INTRINSIC

- 1) genetic causes
 - AD } distal RTA (nephrocalcinosis & stones in 70%)
 - AR } **cystinuria**
 - } **primary hyperoxaluria**
 - } DHA
 - } xanthinuria
 - X-linked } **Lesch-Nyhan**
 - } Dent's disease (stones, hypercalciuric hypophosphatemic rickets, LMW proteinuria with nephrocalcinosis)
 - polygenetic
- 2) urinary constituents
 - **hypercalciuria**
 - **infections**
 - hyperoxaluria
 - cystinuria
- 3) stasis or UTI
 - **anatomic abN'ities** } **UPJO most common anatomic lesions causing stones**
 - **functional abN'ities** } **MMC, neurogenic bladder**
- 4) medical causes
 - **bowel disease** } diversion, diarrhea (dehydration)
 - metabolic acidosis (hypocitraturia)

→ EXTRINSIC

- 1) **low birth weight (<1.5kg)**
 - 30-90% of very LBW babies treated with lasix have stones
 - can occur in kids that have not received lasix
- 2) diet
 - protein/fat
 - salt
 - alkaline-ash (vegetarians with alkaline urine)
 - acid-ash (meat eaters with acidic urine)
- 3) meds
 - stone-forming meds } triamterine, silicate antacids, indinavir
 - stone-facilitating meds } probenecid, salicylates, lasix
 - Na, Ca, or vit D supplementation
 - **steroids**
 - **theophylline**
 - TPN } increases oxalate excretion in LBW babies

What are the side effects of renacidin? → now BANNED

- General
 - } DEATH (likely d/t sepsis)
 - } Perc tract related complication (bleed, collecting system injury, pain, persistent drainage)
 - } extravasation
- Renacidin specific
 - } **↑ Mg** → neuro flat
 - } ↓ DTR
 - } ↓ BP
 - } ↑ PRWT
 - } apnea
 - } met acidosis
 - } mucosal irritation

What are the contraindications to dissolution therapy?

- | | |
|----------------------------|---------------------------------|
| 1) active infection | 5) electrolyte abN'ities |
| 2) fever | 6) renal insufficiency |
| 3) flank pain | 7) immature tract |
| 4) distal obstruction | |

Why do patients with IBD get stones?

→ small bowel resection, Crohn's } Ca oxalate stones most common

- hypercalciuria → from steroids & metabolic acidosis
 - hyperoxaluria → enteric hyperoxaluria } saponification of FA's that bind to Ca, so it can't bind to oxalate, allowing more oxalate absorption in colon
 - irritated mucosa is more permeable to oxalate
 - lack of bacteria (*Oxalobacter formigenes*) due to resorption of bile salts
 - hypocitraturia → from hypoK and intracellular acidosis
 - hypomagnesuria
- nic resection, ileostomy } uric acid stones common**
- dehydration → from malabsorption of water & diarrhea
 - urine acidification

List causes of nephrocalcinosis?

→ CORTICAL

- Cortical necrosis (acute)
- primary **Oxalosis**
- chronic **Rejection**
- **Toxins** (ethylene glycol, etc)
- **Insufficiency** of pyridoxine (B6)
- **Chronic GN**
- **Alport's syndrome**
- sick **Le** cell disease

→ MEDULLARY

- **distal RTA (2nd most common)**
- **MSK (common)**
- sarcoidosis
- excess vitamin D
- renal TB
- renal papillary necrosis
- Dent's disease, Paget's disease
- hypercalcemia
 - **1° hyperPTH (most common)**
 - immobilization
 - malignancy
 - hyperT4
 - pheochromocytoma
 - milk-alkali syndrome
 - Vitamin A, Vitamin D
 - meds (steroids, HCTZ, Li, E)

What are the GU manifestations of sarcoidosis? (AUA Update #14 – 2008)

- > sarcoidosis is more common in F & in blacks
- } non-caseating granulomas of lungs & skin
- } lymphadenopathy (most commonly hilar)

→ “GU SARC Has Pulmonary Nodal Disease”

- 1) **Genital skin lesions** (scrotal, penile)
→ diffuse granulomatous inflammation OR discrete nodules
- 2) **Urolithiasis** (calcium) → 10%
→ can be 1st sign of sarcoidosis
→ hyperCa (10-20%), hypercalciuria (60%) } activated macrophages upregulate 1 α -hydroxylase
resulting in excess 1,25-Vit D (calcitriol)
Rx → steroids down-regulate 1 α -hydroxylase
- 3) **Scrotal mass** (testis, epididymis)
→ testis mass can be mistaken for Ca
- 4) **Azoospermia** (obstructive)
- 5) **RPF**
- 6) **Chronic renal failure** (uncommon)
→ granulomatous interstitial nephritis (GIN)
- 7) **Hematuria**
- 8) **Pseudotumours** (rare)
→ can resemble renal lymphoma
→ if lung nodules, can resemble metastatic RCC \ renal mass in sarcoidosis is
/ more likely to be RCC
- 9) **Nephrocalcinosis** (medullary) → <5%
- 10) **Detrusor areflexia, DSD**
→ from thoracic spinal cord involvement
→ extremely rare but can get bladder lesions } resembles malacoplakia BUT has **asteroid bodies**

What are the selective medical therapies for stones?

- 1) Absorptive hypercalciuria ("T COB")
 - **mainly for type 1** } type 2 often ok with decreased Ca diet + increased fluids alone
 - **thiazides** } **stimulates Ca resorption in DCT** while promoting Na excretion
 - } also decreases serum K and mildly decreases urinary citrate
 - } **doesn't change gut absorption of Ca** } **long-term success is low**
 - } **best if combined w/ K citrate + dietary restriction of Ca & oxalate**
 - S/Es → K wasting, muscle cramps, hyperuricosuria, hypocitraturia, ↓'d libido, sleepiness
 - may unmask or induce primary hyperPTHism
 - usually mild and disappear with continued treatment
 - Cellulose PO₄ } binding resin that decreases Ca absorption
 - } **only recommended if refractory to thiazides**, due to +++ GI S/Es
 - S/Es → hypoMg, PTH stimulation, hyperoxaluria, GI distress
 - Orthophosphate } inhibits Vit D₃
 - ↓'s gut absorption of Ca + ↓'s urinary Ca reabsorption
 - increases urine PO₄ and citrate
 - } **recommended only if refractory to other methods**
 - S/Es → PTH stimulation, hyperoxaluria, GI distress
 - Bran } may decrease intestinal Ca absorption and increase urine PO₄ excretion
- 2) renal leak hypercalciuria
 - **thiazides** } ideal because it increases reabsorption of Ca in distal and proximal tubule
 - } **also give K citrate (K supplementation + increases urine citrate)**
- 3) resorptive (primary hyperPTH) hypercalciuria
 - **PTHectomy** } resection of dominant adenoma or removal of all 4 hyperplastic glands
 - } decreases urinary Ca, gut absorption of Ca, and serum Ca
- 4) hyperuricosuric Ca stones
 - **allopurinol** } inhibits xanthine oxidase, which converts xanthine to uric acid
 - } ↓'s serum & urine uric acid thereby ↓'ing nucleation of Ca oxalate crystals
 - } also increases citrate levels in urine
 - S/Es → rash, myalgia
 - **K citrate** } increases urine pH and urinary citrate
 - S/Es → hyperK, GI upset
- 5) hyperoxaluric Ca stones
 - a) Enteric → **hydration**
 - **Ca supplements** } binds oxalate in gut and prevents absorption
 - **cholestyramine** } binds bile salts and ↓'s gut hyperabsorption of oxalate
 - **K citrate** } corrects hypoK + increases urine citrate
 - b) primary → **pyridoxine** } cofactor in conversion of glyoxylate to glycine & lowers oxalate excretion
 - S/Es → diarrhea, neurotoxicity (with high doses)
 - increased **H₂O intake, K citrate, thiazides, Mg gluconate**
 - **need combined liver & kidney Tx**
 - c) dietary → **decrease dietary oxalate intake**
- 6) hypocitraturic Ca stones
 - **alkalinization**
 - a) distal RTA → **K citrate** } corrects metabolic acidosis & hypoK while ↑'ing urinary citrate
 - b) chronic diarrhea → **liquid K citrate** } faster absorption to offset rapid GI transit
 - states } corrects acidosis from HCO₃ loss & increases urinary citrate
 - c) thiazide-induced → **add K citrate** } supplements lost K and increases urinary citrate
 - d) high protein diet → improve diet
 - e) idiopathic → **K citrate** } increases urinary citrate
- 7) hypomagnesiuric Ca stones
 - also characterized by hypocitraturia + low urine volume
 - **Mg oxide / Mg hydroxide** } increases urine Mg & citrate, decreases urine oxalate
 - } given with K citrate
 - S/Es → GI upset (lots of diarrhea)
 - **K-Mg citrate** } may be better tolerated from GI perspective with same effects

8) gout

- **goal is to increase urine pH above 5.5 (but not too alkaline – preferably 6.5 – 7.0)**
- **Na bicarb** } increases pH of urine BUT can lead to Ca stones
- **K citrate** } increases urine pH & increased citrate means no increase in Ca stones
 } **add allopurinol if** ↑'d urinary uric acid or if hyperuricemia exists

9) cystinuria (“PACK MAB”)

- **hydration** } aim for 2-3 L of u/o per day
 - } try to decrease urine [] of cystine to <250mg/L
- **low-Na diet** } high dietary salt leads to increased cystine excretion
- **K citrate** } increases urine pH to decrease cystine crystal formation
 - but pKa is 8.3 so its hard and at these levels, at risk of Ca PO₄ stones
- **α-mercaptopropionylglycine** } ↑'s cystine solubility by binding to it (S-S bonds)
 - (Thiola) } **less frequent side effects**
 - S/Es → rash, asthenia, GI, joint aches, mental status Δ's
- **Penicillamine-D** } increases cystine solubility in urine by binding to it (S-S bonds)
 - (Cuprimine) } **more frequent side effects but also slightly more effective**
 - S/Es → nephrotic syndrome, dermatitis, pancytopenia
- **captopril** } ACEi that increases cystine solubility by binding to it (S-S bonds)
 - } **least frequent side effects but also least effective**
 - S/Es → fatigue, hypoTN, chronic cough
- **bucillamine**

10) struvite stones

- **surgical management of ALL stone burden** followed by improved bladder health, adequate urinary drainage, and suppressive Abx (**remove then prevent**)
- **acetohydroxamic acid** } urease inhibitor
 - } **for severe cases** → prevents recurrence and inhibits growth
 - } side effects are frequent (20-60%)
 - S/Es → **DVT (15%)**, tremor, H/A, palpitations, edema, rash, GI upset, anemia, alopecia
- hemacidrin } irrigant for dissolution of residual fragments
 - } **not used very often**

List drugs used for cystinuria. }} “PACK MAB”

- chelators (S-S bond)
 - Penicillamine-D
 - Alpha-MPG (thiola)
 - Captopril
- urine alkalinizers
 - K citrate
 - Mucomyst
 - Acetazolamide
 - Bucillamine (chelator)

What types of stones can be treated with dissolution therapy?

- | | |
|---|------------------------------|
| → alkalization (eg K citrate, Na bicarbonate) | → urinary acidification |
| 1) Ca oxalate stones | 1) struvite stones |
| 2) uric acid | 2) Ca PO ₄ stones |
| 3) cystine stones | 3) indinavir stones |
| 4) xanthine stones | |
| 5) ammonium acid urate stones | |

Chapter #43 – Evaluation and Management of Stones

DIAGNOSTIC EVALUATION OF STONES

What are the metabolic problems that cause recurrent stones?

- distal RTA
- primary hyperPTHism
- enteric hyperoxaluria
- cystinuria
- gout

Selection of Patients for Metabolic Evaluation

Which patients should undergo a metabolic evaluation (CHART)?

→ “SICK SAP, U GO FOR URINE” tests

- Solitary kidney
- Intestinal disease → IBD, etc that results in chronic diarrhea
- Cystine stones
- Kids → significantly higher risk of underlying metabolic disease
→ concerns regarding long-term sequelae of recurrent stones - Gout
- Struvite stones
- Anatomic abnormalities
- Pathologic skeletal fractures
- Uric acid stones
- Gout
- Osteoporosis
- Family history
- Occupational } pilots, etc
- Recurrent stone formers → 25% chance of recurrence in 10yrs
→ have higher incidence of metabolic abN'ity than single stone formers (Yagisawa '98)
- UTIs with stones
- Renal insufficiency
- Infirm patients → those not well enough to tolerate repeated attacks of renal colic
- Nephrocalcinosis
- Ethnicity } blacks → lower incidence of stones

Abbreviated Protocol for Low-Risk Single Stone Formers

What is the abbreviated evaluation of low-risk single stone formers (CHART)?

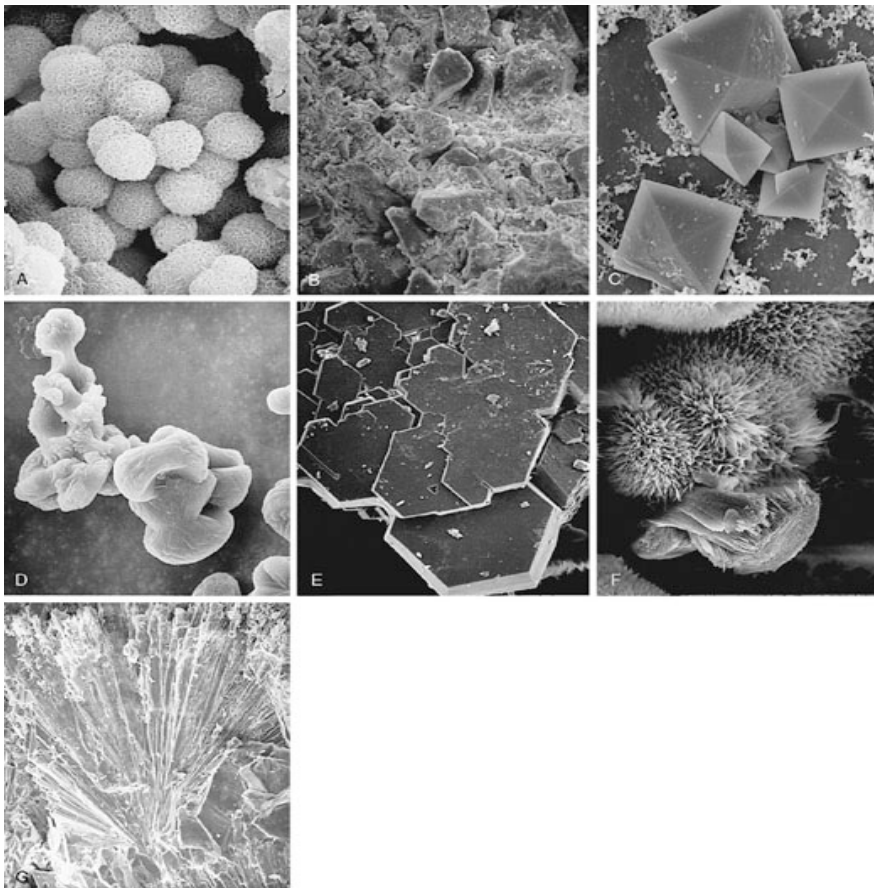
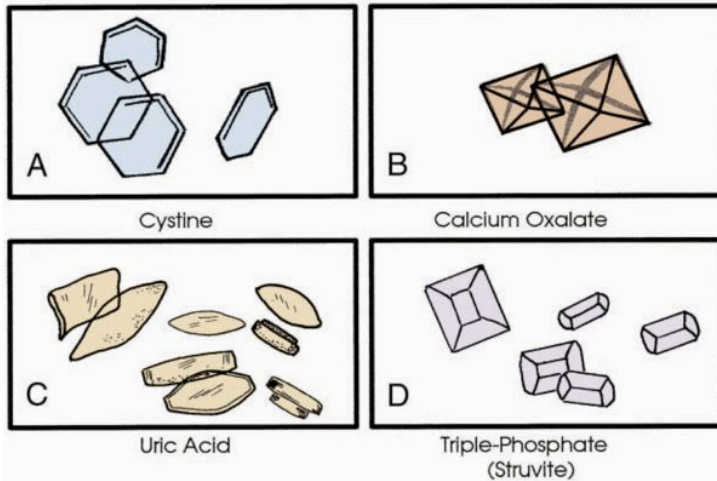
- 1) Hx → current presentation (pain, location, onset, quality, quantity, alleviating/aggravating factors, LUTs, hematuria, N/V, fever, chills, etc)
 - previous stone hx (episodes, when, how many, stone type, management, complications, etc)
 - underlying predisposing conditions (IBD, gout, osteoporosis, UTIs, malignancy, bowel Sx, etc)
 - meds (calcium, Vit C, Vit D, steroids, acetazolamide, antacids, chemo, ACEi), allergies
 - dietary hx (excessive red meat, inadequate fluid intake, excessive fluid losses, etc)
 - social hx (occupation, smoker, EtOH) and family hx
- 2) Physical Exam → general appearance
 - vitals (BP, temp)
 - abdo exam (masses, CVA tenderness, scars, DRE, etc)
 - *** r/o need for immediate stent placement ***
- 3) **bloodwork** → **CBC, lytes, BUN, creatinine, Ca profile, intact PTH, uric acid**
 - primary hyperPTH (high calcium, low PO₄)
 - renal phosphate leak (hypoPO₄)
 - uric acid stones (hyperuricemia)
 - distal RTA (hypoK, acidosis)
 - β-hCG if fertile female
- 4) **urine tests** → **urinalysis**
 - pH >7.5 } infected stones or RTA
 - pH <5.5 } uric acid stones
 - sediment for crystalluria
 - **urine C&S** (urea-splitting stones suggest struvite stones)
 - **qualitative cystine**
- 5) imaging → KUB
 - radiolucent ("U Don't See The Xray IMAGE") } uric acid, xanthine, triamterene, etc
 - radio-opaque } Ca oxalate, Ca PO₄, struvite [Mg ammonium PO₄], cystine
 - IVP (radiolucent stones, anatomic abnormalities)
 - noncontrast spiral CT
 - renal function if thin parenchyma
- 6) stone analysis

List 3 advantages & 3 disadvantages of CT over IVP for diagnosing urinary stones

- advantages
 - more sensitive & accurate at diagnosing stones
 - can see other anatomic pathology
 - faster
 - no exposure to contrast
 - not contraindicated in renal failure
- disadvantages
 - more radiation
 - more expensive
 - may not provide as detailed anatomy of collecting system
 - does not give info about renal function (uptake & excretion)
 - may confuse with phlebolith

What do common stone types look like under microscopy (CHART)?

- Ca phosphate-apatite } amorphous
 - Ca PO₄ dihydrate (brushite) } needle-shaped
 - COM } hourglass/dumbbells
 - COD } tetrahedral, envelope
 - struvite } rectangular, coffin-lid
 - cystine } hexagonal (benzene)
 - uric acid } amorphous shards, plates
- brushes have needle-shaped bristles
 - you'd be a dumbbell to SWL COM stones
 - Cash-On-Delivery when your envelope arrives
 - dead in a coffin if you get struvite stones
 - you are Hex'd since birth with cystine stones
 - shards of uric acid



- A – apatite
 - amorphous
- B – struvite
 - coffin-lid
- C – COD
 - envelope
- D – COM
 - dumbbell
- E - cystine
 - hexagonal
- F – ammonium urate
- G – brushite (CaPO₄ dihydrate)
 - needle

Extensive Diagnostic Evaluation *** NOT DONE OFTEN ***

Which patients should undergo an extensive diagnostic evaluation?

- 1) recurrent stone formers
- 2) high-risk single stone formers

What is the extensive diagnostic evaluation?

- involves 2 visits → stop all meds that could interfere with Ca, uric acid or oxalate metabolism (Vit D, Ca supplements, antacids, diuretics, acetazolamide, Vit C)
→ stop all stone treatment meds (thiazides, PO₄, allopurinol, Mg)
- get three 24-hr urine samples → 2 on 1st visit (usual diet)
→ 1 on 2nd visit (Ca-, Na-, and oxalate-restricted diet)
→ discard first AM void, and collect for 24hrs
→ **check urine creatinine to validate collection**
 - men } 15-20 mg/kg/day
 - women } 10-15 mg/kg/day
- bloodwork → CBC, lytes, BUN, creatinine, intact PTH, Ca, uric acid } each visit
- urine tests → pH, lytes, total volume, oxalate, citrate, qualitative cystine } each visit
- fast and Ca load test → urine collection done on morning of 2nd visit
→ helps to differentiate b/w absorptive, renal leak & resorptive hypercalciuria

Describe how a fast and Ca load test is done.

- restricted diet for 1 week prior
- distilled water 12hrs and 9hrs prior
- fasting for 12 hours prior
- empty bladder completely 2 hours before calcium load and drink 600mL distilled water
- collect all urine during next 2 hours (fasting urine)
- ingest 1g oral calcium load in 250mL solution over 5-10 minutes
- urine collected over next 4 hours (post-load urine)
- compare urine for excreted calcium

***** NOT done very often because treatment for both absorptive and renal leak hypercalciuria are similar ... essential if planning on prescribing Ca-binding resin for absorptive *****

Simplified Metabolic Evaluation

What is the simplified metabolic evaluation?

- 1) Hx & Physical
- 2) collect one or two 24-hr urine samples
 - no consensus on 1(Pak et al) or 2 (Rivers et al, Parks et al)
 - if 2 then one would be on usual diet, the other on a restricted diet
 - **good collection } 10-15 mg/kg/day creat for F & 15-20 mg/kg/day creat for M**
- 3) **urine for Ca, oxalate, uric acid, citrate, cystine, pH, total volume, Na, Mg, K, sulfate**
 - "COUCCH" + lytes
 - no fast and Ca load test
- 4) **bloodwork**
 - **CBC, lytes, BUN, creat, intact PTH, Ca panel, uric acid**
- 5) imaging
- 6) stone analysis (helps obviate need for complete metabolic work-up)

What is the classification of stones?

- Table 43-11 -- Diagnostic Criteria

[illegible]

Calcium-based Stones

What are the causes of Ca-based stones?

1) hypercalciuria (>200 mg/day)

- a) absorptive → **N serum Ca + N or suppressed PTH + N fasting urinary Ca (most)**
 - type 1 } regardless of amount of Ca in diet
 - type 2 } normal urinary Ca when on Ca-restricted diets
- b) renal leak → impaired PCT reabsorption of Ca, regardless of diet
 - **N serum Ca + ↑ PTH + ↑ fasting urinary Ca + ↑ Vit D**
- c) resorptive (primary hyperPTH) → from adenoma or diffuse hyperplasia of 4 glands
 - **hyperCa + ↑ PTH + ↑ fasting urinary Ca + ↑ Vit D**
- d) idiopathic primary

2) hypocitraturic (<550mg female, <450mg male)

- systemic acidosis is primary determinant of urinary citrate excretion
- a) distal RTA (type 1) → acquired or inherited form } 80% are women
 - incomplete form is milder
 - **hypocitraturia (<100mg/day) + high urine pH (>6.5)**
 - + **hypercalciuria + hyperphosphaturia**
 - **serum hypoK, hyperCl, non-anion gap metabolic acidosis,**
 - 70% of adults have stones ... kids present with N/V, diarrhea, growth retardation, FTT
- b) chronic diarrhea → **mildly elevated urinary oxalate (unlike enteric hyperoxaluria)**
 - + **mildly low urine citrate + low urine volumes**
- c) thiazide-induced → **hypocitraturia** from hypoK + resulting intracellular acidosis
- d) high-protein diet } acid load
- e) idiopathic → r/o incomplete distal RTA with NH₄ chloride loading challenge

3) hyperuricosuric (>600 mg/day)

- prone to Ca oxalate stones from heterogeneous nucleation (epitaxy)
- may have high serum uric acid +/- gout
- 1) dietary excess of purines (most common cause)
- 2) uric acid overproduction } gout, myeloproliferative & lymphoproliferative d/o's, hemolytic d/o's, multiple myeloma, hemoglobinopathies and thalassemia

4) hyperoxaluric (>40 mg/day)

- a) primary → AR inborn error of metabolism
 - type 1 & 2 } presents in childhood with stones, renal failure from nephrocalcinosis, and tissue deposits of oxalate
 - } death by age 20 if untreated
 - **elevated serum & urine oxalate**
- b) enteric → chronic diarrhea, gastric bypass
 - **hyperoxaluria + acidic urine pH (loss of bicarb) + hypocitraturia (acid-base buffer) + dehydration (low urine volume)**
- c) dietary → tea, cocoa, spinach, beets, okra, some berries, chocolate, nuts, soy crackers, etc
- d) idiopathic

5) hypomagnesiuric (<80mg)

- **low urine Mg + hypocitraturia + low urine volume**
- often assoc'd w/ IBD & chronic thiazide Rx } may actually be d.t. concomitant hypocitraturia

List the causes of acquired distal RTA (CHART). } } } "POST CLAAASHH"

- Cirrhosis
- Lithium
- Analgesic abuse
- ATN
- Autoimmune disease } thyroiditis, SLE, Sjogren's
- Sarcoidosis
- Hypercalciuria (familial)
- HyperPTHism
- Pyelo (chronic)
- Obstruction (chronic)
- Sick cell
- Transplant

Table 43-6 -- Differential Diagnosis of Hypercalciuria

	Absorptive	Renal	Resorptive
Serum calcium	Normal	Normal	Elevated
Parathyroid function	Suppressed	Stimulated (secondarily)	Stimulated (primarily)
Fasting urinary calcium	Normal	Elevated	Elevated
Intestinal calcium absorption	Elevated (primarily)	Elevated (secondarily)	Elevated (secondarily)

Uric acid-based Stones

What are the findings of patients with uric acid stones?

- urine pH <5.5 (pKa)
- radiolucent stones
- hyperuricemia
- tend to make lots of small stones ... orange in colour on endoscopy
- produce small amounts of **cyanide on laser lithotripsy**

What types of stones are formed by those with hyperuricosuria?

→ **no known inhibitors of uric acid crystallization**

- 1) uric acid stones } has pH <5.5
- 2) Ca oxalate stones } normal urine pH +/- hypercalciuria

What are the RFs for uric acid stone formation? }} “They Make GOLDD’N PeePee”

- 1) **T**halessemia
- 2) **M**yeloproliferative disorder
- 3) **G**out
- 4) **O**besity
- 5) **L**esch-Nyhan
- 6) **D**M
- 7) **D**ehydration
- 8) **N**eoplastic disease
- 9) **P**urine-rich diet → red meat
- 10) **P**regnancy

Cystine stones

How do cystine stones form?

- error of transepithelial transport involving intestine & kidneys (**AR inheritance**)
 - can’t reabsorb amino acids (**Cystine, Ornithine, Lysine, Arginine**)
- cystine crystallizes when concentration in urine is >250 mg/L
- usually present at young age with +ve family hx of stones
- **low/acidic urine pH**
- often associated with **hypocitraturia, hypercalciuria & hyperuricosuria**

Describe cystine stones?

- yellow and waxy in appearance
- faintly radio-opaque
- common to get staghorn calculi
- produce **sulfuric gas on laser lithotripsy**

Struvite Stones

How do struvite stones form?

- alkaline urine (**pH usually >6.5-7.0**) } environment rich in ammonia (from urea-splitting bacteria)
- more common in F and in patients with neurogenic bladders
- most common type of staghorn stone

How do struvite stones usually present?

- weakness, malaise
- flank pain
- LUTS +/- hematuria
- staghorn stone
- fever
- dysuria
- XGP
- loss of appetite

What is the most common composition of staghorn stones?

- 1) **struvite (most common - 67%)**
 - 2) cystine
 - 3) uric acid
 - 4) COM
- **isolated CaPO₄ is likely the least common to form staghorn**

What are the RFs for development of struvite stones? }}} “Urine Can OFFEND People”

→ those at risk for infections

- Urinary diversion
- Congenital GU tract anomaly
- Obstructed GU tract
- Female
- FB (eg foley)
- Elderly
- Neurogenic bladder
- DM
- Premature infants

Low urine volumes

What is the significance of low urine volumes?

- concentrates urine & raises risk of supersaturation
- **tends to result in acidic urine → acidic urine also consumes buffers such as citrate**

No Disturbances

How common are stone formers found to have no metabolic abnormalities?

- found in 3% of patients } must r/o error in collecting 24hr urine sample

What are the potential causes of an erroneous 24hr urine collection?

- 1) error in collection technique → improper use of preservatives, ice
- 2) failure to collect a full 24hrs' worth of urine
- 3) changes in diet during study
- 4) intermittent indiscretions in diet
- 5) failure of specimen to accurately represent a “typical day”
- 6) bacterial contamination

THE ECONOMICS OF METABOLIC EVALUATION

What are the most economical management strategies for stone patients?

- 1) first-time stone formers → conservative management (lifestyle, diet)
→ no metabolic w/u unless high-risk
- 2) recurrent stone formers → simplified metabolic w/u + directed medical Rx is 1st choice

USE OF STONE ANALYSIS TO DETERMINE METABOLIC ABNORMALITIES

How can stone analysis help with treatment?

- stone composition can help predict metabolic abnormality
 - eg Ca PO₄ and Ca apatite stones likely mean distal RTA or primary hyperPTHism
 - eg pure struvite stones don't need further w/u
- stone composition can predict supersaturation values

What are some common mineralogic names for renal stones (CHART)?

- Mg ammonium PO₄ → struvite
- Ca oxalate monohydrate (COM) → whewellite
- Ca PO₄ → brushite
- Ca oxalate dihydrate (COD) → weddellite

CONSERVATIVE MEDICAL MANAGEMENT

What conservative recommendations should be made to first-time, low-risk stone formers?

→ "Stone Formers Placed On Weight Control"

1) Fluid recommendations

- **increase fluid intake to achieve daily u/o of ≥2L** } decreases stagnation & increases Kf
- water hardness doesn't really help much } soft water slightly worse
- **carbonated water may be slightly protective** } increases urinary citrate
- soda + citric acid (eg lemonade/OJ) may ↓ risk, but soda + phosphoric acid may ↑ risk

2) dietary Sodium and Protein

- **Na restriction ↓'s risk of Ca stones** } confirmed on randomized trials
 - high Na diet ↑'s crystallization of Ca in urine
 - decreases stone episodes by ~50%
- **moderated animal protein (meat) is better** } confirmed on randomized trials
 - protein increases urinary Ca, oxalate, and uric acid → Atkins diet bad!!!

3) Ca in diet

- **moderate Ca diet is best** } restricted Ca diet increases oxalate absorption from gut
- **Ca citrate is best supplement** } high urine citrate offsets higher urine Ca

4) Oxalate in diet

- **only 10-15% of urinary oxalate is from diet** } rest from liver
 - role of dietary changes is debatable
- **avoid excess dietary oxalate** (chocolate, tea, beets, spinach, nuts)
- limit Vit C to <2g/day } Vit C (ascorbic acid) is converted to oxalate

5) Weight

- increased BMI, larger waist size, & weight gain associated w/ increased risk for stones
- increased risk more pronounced in F
- **obese patients at higher risk of forming Ca & uric acid stones } urine is acidic**
 - diabetics have impaired NH₄ as well
- low-carb, high-fat diets increase acid load to kidney and increases stone formation
 - Atkins, South Beach diets bad!!!
- bariatric surgery associated with increased risk of stones } increased urine oxalate

***** moderate Ca diet + salt restriction + moderation of animal protein resulted in 50% less stones compared to Ca-restricted diets *****

What is the f/u after conservative medical management is initiated?

- re-evaluate pt (serum, urine) after 3-4 month trial of conservative mgt
- if conservative Rx has corrected patient's metabolic or environmental abN'ities, continue and re-evaluate in 6-12 months
- if metabolic defect persists, selective medical Rx may be instituted

SELECTIVE MEDICAL THERAPY FOR STONES

What are the selective medical therapies for stones?

- 1) Absorptive hypercalciuria ("Ty COB")
 - **mainly for type 1** } type 2 often ok with decreased Ca diet + increased fluids alone
 - **Thiazides** } stimulates Ca resorption in DCT & promotes Na excretion
 - (1st line) } also decreases serum K and mildly decreases urinary citrate
 - } **doesn't change gut absorption of Ca** } **long-term success is low**
 - } **should be combined with K citrate + dietary restriction of Ca & oxalate**
 - } could also use chlorthalidone, indapamide, trichlormethidazide, amiloride + HCTZ
 - S/Es → **hypoK**, muscle cramps, **hyperuricosuria**, **hypocitraturia**, ↓'d libido, sleepiness
 - usually mild and disappear with continued treatment
 - may unmask or induce primary hyperPTH'ism
 - Cellulose PO₄ } binding resin that ↓'s Ca absorption → also binds to Mg (need supplements)
 - } **only recommended if refractory to thiazides, due to +++ GI S/Es**
 - S/Es → **hypoMg, hyperoxaluria**, PTH stimulation, GI distress
 - Orthophosphate } inhibits Vit D₃
 - ↓'s GI absorption of Ca & urinary Ca excretion + ↓'s urine Ca-oxalate saturation
 - ↑'s urine PO₄ (**contraindicated in struvite stones**), oxalate & citrate
 - } **recommended only if refractory to other methods**
 - S/Es → PTH stimulation, hyperoxaluria, GI distress, soft tissue calcification
 - Bran (rice) } may decrease intestinal Ca absorption and increase urine PO₄ excretion
- 2) renal leak hypercalciuria
 - **thiazides** } ideal because it increases reabsorption of Ca in distal & proximal tubule
 - } **also give K citrate (K supplementation + increases urine citrate)**
 - } does have **good long-term success**
- 3) resorptive (primary hyperPTH) hypercalciuria
 - **PTHectomy** } resection of dominant adenoma or removal of all 4 hyperplastic glands
 - } decreases urinary Ca, gut absorption of Ca, and serum Ca
- 4) hypocitraturic Ca stones
 - **alkalinization**
 - a) distal RTA → **K citrate** } corrects metabolic acidosis & hypoK while ↑'ing urinary citrate
 - b) chronic diarrheal states → **liquid K citrate** } faster absorption to offset rapid GI transit
 - } corrects acidosis from HCO₃ loss & ↑'s urinary citrate
 - c) thiazide-induced → **add K citrate** } supplements lost K and increases urinary citrate
 - d) high protein diet → improve diet
 - e) idiopathic → **K citrate** } increases urinary citrate
- 5) hyperuricosuric Ca stones
 - decreased dietary purine intake
 - **allopurinol** } inhibits xanthine oxidase, which converts xanthine to uric acid
 - } ↓'s serum & urine uric acid thereby ↓'ing nucleation of Ca oxalate crystals
 - S/Es → rash, myalgia
 - **K citrate** } increases urine pH & urinary citrate
 - S/Es → **hyperK, GI upset**
- 6) hyperoxaluric Ca stones
 - increased fluids for all
 - a) Enteric → **hydration + low oxalate, low fat diet**
 - **Ca supplements** } binds oxalate in gut & prevents absorption BUT also get hypercalciuria
 - **cholestyramine** } binds bile salts thereby ↓'ing colonic hyperabsorption of oxalate
 - **K citrate or Mg citrate** } corrects hypoK + increases urine citrate (and Mg)
 - b) primary → **pyridoxine (B6)** } cofactor in conversion of glyoxylate to glycine & ↓'s oxalate excretion
 - S/Es → diarrhea, neurotoxicity (with high doses)
 - **increased H₂O intake, K citrate, thiazides, Mg gluconate**
 - **need combined liver and kidney Tx**
 - c) dietary → **decrease dietary oxalate intake**

→ enteric hyperoxaluria (“HONK My CIC”)	→ primary hyperoxaluria (“Hong Kong? Don’t TEMPT”)
<ul style="list-style-type: none"> - Hydration - Oxalate restriction - Na restriction - K citrate - Mg supplements - Ca supplements - Iron - Cholestyramine 	<ul style="list-style-type: none"> - Hydration - K citrate - Dialysis - Thiazides - Elmiron - Mg gluconate - Pyridoxine (B6) - Transplant (liver + kidney)

List ways allopurinol decreases stone formation.

- ↓'s uricosuria
- ↑'s urine pH (alkalinization)
- ↑'s urinary citrate levels

List drugs used for cystinuria. } } } “PACK MAB”

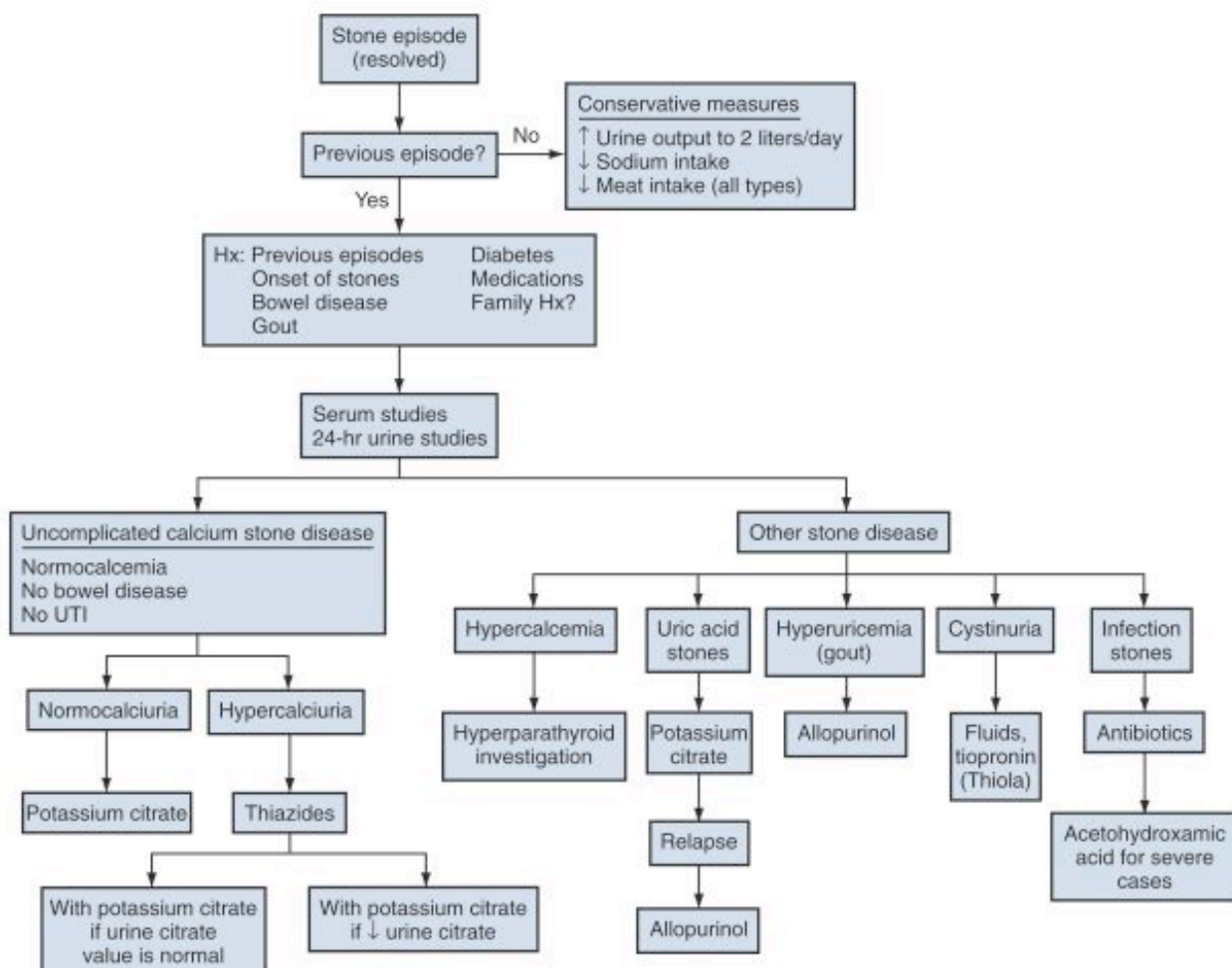
- chelators (S-S bond)
 - **P**enicillamine-D
 - **A**lpha-MPG (thiola)
 - **C**aptopril
 - **B**ucillamine
- urine alkalinizers
 - **K** citrate
 - **M**ucomyst
 - **A**cetozolamide

Table 43-13 -- Physicochemical and Physiologic Effects of Pharmacologic Therapy

	<i>Sodium Cellulose Phosphate</i>	<i>Orthophosphate</i>	<i>Thiazide</i>	<i>Allopurinol</i>	<i>Potassium Citrate</i>
Urinary calcium	Marked decrease	Mild decrease	Moderate decrease	No change	Mild decrease or no change
Urinary phosphorus	Mild increase	Marked increase	Mild increase or no change	No change	No change
Urinary uric acid	No change	No change	Mild increase or no change	Marked decrease	No change
Urinary oxalate	Mild increase	Mild increase	Mild increase or no change	No change or mild decrease	No change
Urinary citrate	No change	Mild increase	Mild decrease	No change	Marked increase
Calcium oxalate saturation	Mild decrease or no change	Mild decrease	Mild decrease	No change	Moderate decrease
Brushite saturation	Moderate decrease	Mild increase	Mild decrease	No change	No change

Table 43-15 -- Potential Side Effects of Medications Used to Prevent Urinary Lithiasis

Medication	Side Effect
Thiazide diuretics: hydrochlorothiazide, chlorthalidone, indapamide	Potassium wasting, muscle cramps, hyperuricosuria, intracellular acidosis, hypocitraturia
Sodium cellulose phosphate	Gastrointestinal distress, hypomagnesemia, hyperoxaluria, parathyroid hormone stimulation
Orthophosphate	Similar to sodium cellulose phosphate, soft tissue calcification
Potassium citrate	Gastrointestinal upset, hyperkalemia
Allopurinol	Rash, myalgia
Magnesium gluconate	Diarrhea
Pyridoxine (B6)	Diarrhea
d-Penicillamine	Nephrotic syndrome, dermatitis, pancytopenia
α -Mercaptopyrionylglycine	Rash, asthenia, rheumatologic complaints, gastrointestinal distress, mental status changes
Captopril	Rash, cough, hypotension
Acetohydroxamic acid	Thromboembolic phenomena, tremor, headache, palpitations, edema, gastrointestinal distress, loss of taste, rash, alopecia, anemia, abdominal pain



→ SIMPLIFIED TREATMENT ALGORITHM FOR STONES

MISCELLANEOUS SCENARIOS

What are some medication-related stones?

1) meds that directly form stones (ALL RADIOLOGIC) } } } "Silicates GET SIC"

- **Silicates** (eg Mg silicate antacids) → stones form w/ consumption of large amounts
- **Guaifenesin** (expectorant) → metabolite forms stone
- **Ephedrine** (cold meds, herbal ecstasy, Ma Huang, etc) → metabolite forms stones
- **Triamterene** (K⁺ sparing diuretic) → usually incorporates onto existing stone/nidus
→ doesn't usually form pure triamterene stone
(triamterene or its sulfate metabolite)
- **Septra** (TMP-SMX)
- **Indinavir** (protease inhibitor) → high urinary excretion & poor solubility at N urine pH
→ more soluble at pH <5.5
→ radiolucent even on CT
- **Cipro**

2) meds that indirectly promote stone formation } } } "Can PLATE FAST"

- **Cytotoxic agents** → high cell turnover and increased uric acid stones
- **PO₄-binding antacids** → hypercalciuria
- **Laxatives** → persistent diarrhea leads to ammonium acid urate stones
- **Acetazolamide** (carbonic anhydrase inhibitor) → metabolic acidosis + urinary alkalization,
→ results in hypocitraturia (CaPO₄ stones)
- **Thiazides** → intracellular acidosis and subsequent hypocitraturia
- **Excess Vit C or D** → hypercalciuria
- **Furosemide** → hypercalciuria
- **Allopurinol** → high doses can lead to xanthine stones
- **Steroids** → hypercalciuria
- **Topiramate** (antiepileptic) → acts like a carbonic anhydrase inhibitor

What types of stones can be treated with dissolution therapy?

→ alkalization (eg K citrate, Na bicarbonate)

→ urinary acidification

- 1) Ca stones
- 2) Ca oxalate stones
- 3) uric acid
- 4) cystine stones
- 5) ammonium acid urate stones

- 1) struvite stones
- 2) Ca PO₄ stones
- 3) indinavir stones

List complications of urinary alkalization.

- CaPO₄ stones
- struvite stones
- hyperK (K citrate)
- volume overload (Na HCO₃)
- GI upset, flatulence

What is the medical management of bladder stones?

- usually occurs in older men with BPH, strictures, neurogenic bladder, bladder diverticulum
- usually **uric acid (noninfected) or struvite (infected)**
→ Ca or cystine stones likely came down from ureter
- often associated with intermittent, painful voiding with terminal hematuria
- most can be removed endoscopically

Rx → mainstay of treatment is to relieve BOO

- Suby G/M or Renacidin } irrigate indwelling S/P or Foley to decrease & prevent encrustation
- acetic acid irrigation } for struvite stones
- alkaline solution } for uric acid stones

What are the side effects of renacidin?

→ general

- death } likely from infection not Rx (sepsis)
- percutaneous tract complications } bleeding, collecting system injury, pain, etc

→ specific

- **hyperMg** } decreased BP, decreased reflexes, apnea
- metabolic acidosis
- mucosal irritation

What are the contraindications to dissolution therapy?

- 1) active UTI ***
- 2) fever
- 3) flank pain
- 4) distal obstruction
- 5) *electrolyte abnormalities*
- 6) decreased renal function
- 7) immature tract

What are ammonium acid urate stones?

- most commonly mixed stone composition
- rarely seen in industrialized nations
- associated with **laxative abuse, IBD, ileostomy, obesity, UTIs, hx of uric acid stones**

Rx → stop laxatives

→ treat chronic UTIs

→ hydration + Ca supplements + alkalinization

What are the potential causes of prostatic stones?

→ Ca PO₄ stones

- RADs
- TURP
- cryotherapy
- prostatic stents

What is the medical management of neonatal stones?

- present with hematuria, worsening renal function, calcific densities on xray, nephrocalcinosis
- **often due to lasix or dehydration**
- **may be associated with:**
 - **low birth weight**
 - **prematurity**
 - **TPN**
 - **sepsis**
 - **steroids**
 - **RTA**
 - **cystinuria**
 - **congenital hyperPTHism**

Rx → stop lasix

→ thiazides } doesn't reverse situation but allows kidneys to heal & clear Ca deposits

→ **low Ca/creatinine ratio is best predictor of resolution**

What is the medical management of stones in kids?

- r/o inherited genetic disorder → cystinuria, distal RTA, primary hyperoxaluria
- hard to interpret 24hr urine collections } **urine Ca/creatinine ratio >0.2 is abN**

Rx → similar fluid and diet recommendations as adults

→ hypercalciuria } fluids + Na restriction +/- thiazides

→ cystinuria } fluids + K citrate alkalinization (cystine S-S binders used very rarely)

What is the medical management of stones during pregnancy?

- **no increased risk of stone formation** → urine Ca increases BUT so does urine citrate
- **no role for metabolic w/u until after delivery when physiologic changes normalize**
- U/S is first line imaging modality
 - hard to see distal ureters
 - hydro of pregnancy may be confused with obstruction
- threshold of radiation is 1.2 rad
 - avoid radiation esp in T1 (organogenesis)
- limited IVP (scout + 30 sec + 20-30mins) can be done
 - each film is 0.1 to 0.2 rad
- 66-85% of pregnant women spontaneously pass stones if treated conservatively
 - hydration + analgesics +/- ABx
- if stents needed, use minimal fluoro or use ultrasound
 - stents can migrate down easier with dilated ureters
 - stents encrust easier so should be changed q4-6 weeks
 - **think of percutaneous NT if early in pregnancy (before 22wks)**
- URS + laser litho is safe
 - avoid U/S lithotripter } risk of fetal hearing loss
- **SWL contraindicated**

How does acute renal colic present? (AUA Update #30 - 2008)

- symptoms & symptoms
 - acute onset flank pain +/- radiating to lower abdomen/groin/testicle/labia
 - N/V (celiac plexus)
 - storage LUTS
 - no improvement with movement or positioning
 - CVA tenderness
 - tachycardia (non-specific)
 - elevated BP (non-specific)
 - low grade fever
- lab investigations
 - mild leukocytosis ($<15,000/\text{mm}^2$)
 - mildly elevated BUN and/or creatinine (bilateral stone, solitary kidney, dehydration)
 - hypoK (vomiting)
 - microscopic hematuria (absence does NOT r/o stone)
 - mild pyuria

What CT findings are suggestive of ureteral obstruction (current or recent)? (AUA Update #30 - 2008)

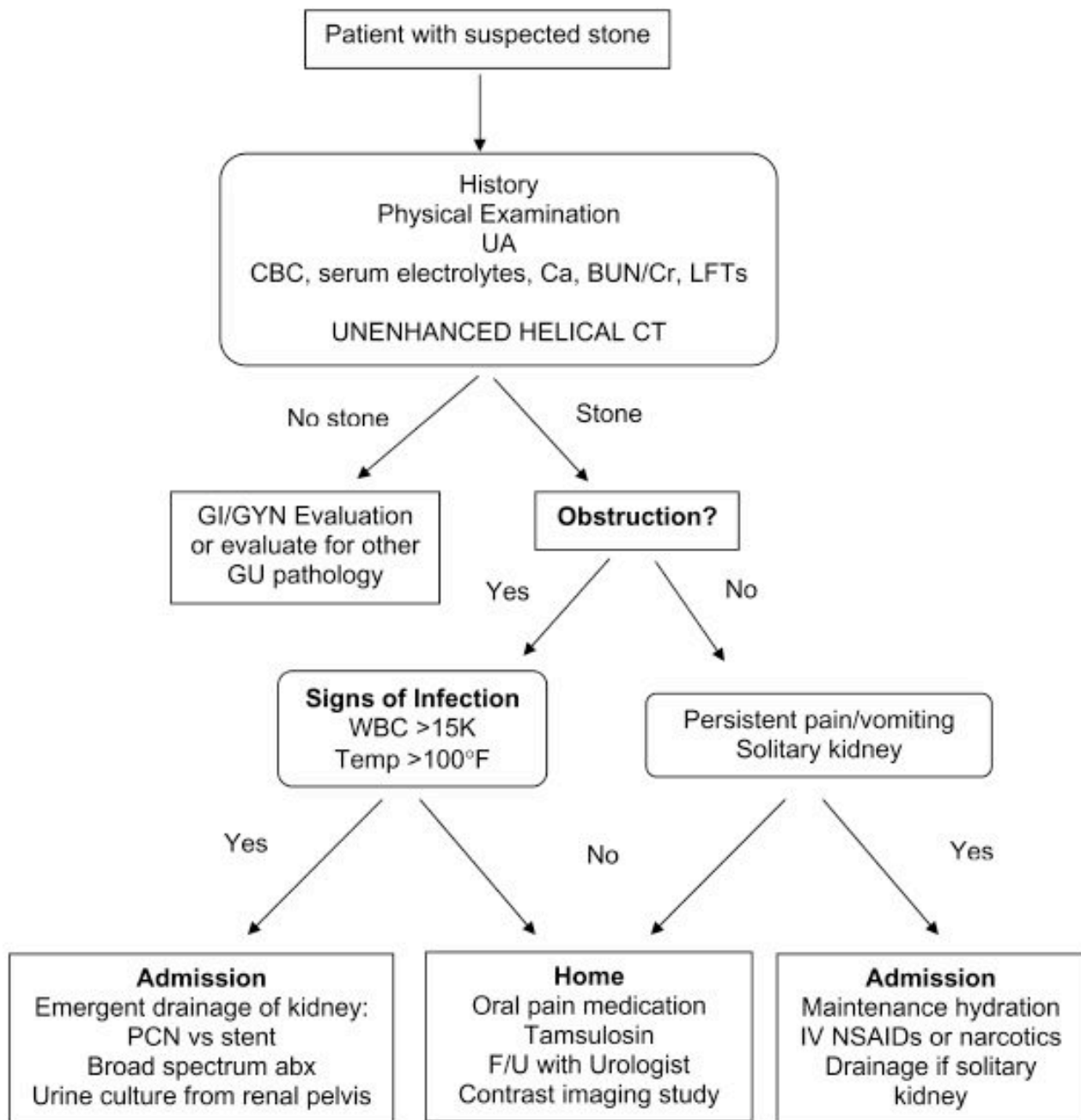
- CT shown to be better than IVP in diagnosing acute renal colic (Worster et al '02 – meta-analysis)
- hydronephrosis
- hydroureter
- peri-ureteric stranding
- UVJ edema

What findings on U/S may suggest acute renal colic in pregnant patients? (AUA Update #30 - 2008)

- difficult to distinguish from physiologic hydronephrosis of pregnancy
- color Doppler RI of >0.7 on symptomatic side (good PPV but if <0.7 , does not r/o obstruction)
- absence of ureteric jets on symptomatic side
- hydroureter with tapering to N caliber ureter above or below pelvic brim

What are contraindications to ketorolac in acute renal colic? (AUA Update #30 - 2008)

- past or current renal insufficiency
- past or current GI bleed
- hypersensitivity to ASA or NSAIDs
- nursing or pregnant women
- bleeding disorder



Algorithm for management of renal colic

SUMMARY

How successful is selective medical therapy for stones?

- better than general therapy
- 80% remission rate
- >90% overall reduction in stone formation rate
- continued compliance and interval reassessments are essential to long-term success

Chapter #44 – Surgical Management of Stones

HISTORICAL OVERVIEW

Where is Brodel's line?

- relatively avascular plane just posterior to the midline of the kidney, along the convex border

What is an anatomic nephrolithotomy?

- described by Smith and Boyce in 1968
- incising kidney along Brodel's line, between the anterior & posterior vascular distributions
- good stone-free rates but high morbidity

RENAL STONES

What are the minimally invasive treatment modalities available for treatment of stones?

- SWL
- ureteroscopy
- PNL
- laparoscopic stone surgery

What are the factors one must consider in deciding the management of kidney stones (CHART)?

1) Stone Factors

- a) stone burden (size & number) } probably most important factor in Rx decision
- b) composition
- c) location

2) Renal Anatomic Factors

- a) obstruction or stasis
- b) hydronephrosis
- c) UPJO
- d) calyceal diverticulum
- e) horseshoe kidney
- f) renal ectopia or fusion
- g) LP location

3) Patient/Clinical Factors

- a) infection
- b) obesity
- c) body habitus deformity
- d) coagulopathy
- e) juvenile
- f) elderly
- g) HTN
- h) renal failure

What pre-op investigations are necessary prior to stone treatment?

- 1) imaging } KUB + noncontrast CT
 } +/- radionuclide studies, retrograde studies
- 2) urine tests } urine C&S

→ stone culture or renal pelvic urine culture is best predictor of post-PNL urosepsis (better than voided C&S)

- 3) stone analysis of previously passed stones

What is the natural history of calyceal stones?

- most will grow in size, become symptomatic or infected, and require intervention
- stones >4mm will likely fail observation
- observation may likely result in more invasive Rx than early treatment

→ **consensus conference**

- 1) the role of prophylactic Rx of small (<5mm), non-obstructive, asymptomatic calyceal stones is not clear
- 2) patients should at least have regular follow-up as most will require intervention

Which patients with asymptomatic CALYCEAL stones should be treated?

- 1) kids
- 2) patients with solitary kidney
- 3) high-risk professions (eg pilots)
- 4) women considering pregnancy

What are staghorn stones?

- stones that fill the renal pelvis and extend into the calyces
- most staghorn stones are **struvite (most common)** or cystine, uric acid, COM

What are the most common causes of staghorn stones?

- **struvite (67%)**
 - cystine
 - uric acid
 - COM
- **CaPO₄ is least likely to form staghorn stones**

How are staghorn stones classified?

- older way } complete → 80% of collecting system + involvement of all calyces
- } partial → renal pelvic stone extending into 2 calyceal groups
- newer way } volume estimation using CT scan + 3D reconstruction

What is the natural history of staghorn stones?

- will eventually lead to renal failure
- untreated patients have ~30% 10yr mortality vs 7% for those treated by surgical intervention
- **2005 AUA guidelines** → all newly diagnosed staghorn stones should be treated surgically
- complete stone removal is essential

What factors predict renal deterioration in patients with staghorn stones?

- solitary kidney
- previous stones
- stone burden (partial vs complete staghorn)
- urinary diversion
- neurogenic bladder
- stone recurrence
- recurrent infections

List common bacteria that can lead to staghorn stones

- Proteus
- Klebsiella
- Pseudomonas
- S. aureus
- mycoplasma

Stone Factors

What stone factors should be considered in deciding Rx modality for stones?

- a) **stone burden (size & number)** } **probably most important factor in Rx decision**
- b) **composition**
- c) **location**

What are the different ways of reporting stone treatment success?

→ **stone clearance, and not fragmentation, is the primary limiting factor**

- 1) “stone free” → most rigorous definition of success
- 2) “insignificant residual fragments” → asymptomatic, small stones (varies from 2-5mm)
- 3) effectiveness quotient →
$$\frac{\% \text{stone free}}{100\% + \% \text{retreatment} + \% \text{auxiliary procedures}} \times 100$$
 (Clayman et al, '89)

What is the effect of stone burden on stone treatment?

- with increasing size & number } ↓'ing stone-free rates
- } ↑'ing retreatment rates and need for ancillary procedures
- **with increasing size & number, PNL becomes more efficient than SWL & ureteroscopy**

What is the treatment algorithm of stones, based on size?

- 1) **≤10mm → SWL is 1st line, regardless of composition or location** } 80% stone-free rates
→ URS and PNL reserved for SWL failure or special situations
- 2) **10-20mm → SWL usually 1st line** } 65% stone-free rates
→ URS or PNL recommended if any factors predicting poor results
(eg LP stone, cystine/brushite/COM stone, etc)
- 3) **>20mm → PNL is 1st line, followed by SWL if necessary** } 90% stone-free rate
→ URS if specific indications (eg bleeding disorder, obesity, etc)
→ SWL + stent is an option but must warn patient of high retreatment rates
- only 50% stone-free rate with SWL

What are the goals of staghorn stones management?

- usually struvite stones } can also be cystine, uric acid, COM
- 1) complete surgical removal of stone burden → residual fragments may lead to stone regrowth
- 2) identify & Rx any metabolic abN'ities → mixed struvite staghorn formers more likely to have metabolic abN'ity than pure struvite
- 3) correct any anatomic abnormalities contributing to urinary stasis

What is the treatment algorithm for staghorn stones?

→ **ALL OPTIONS MUST BE DISCUSSED as per 2005 AUA GUIDELINES**

- 1) PNL → 80% stone-free rate
→ slightly higher when combined with SWL (~85%)
 - PNL + SWL + PNL } needed less now with more flexible nephroscopy (sandwich) } best option for most patients with struvite staghorns
- 2) SWL → only 50% stone-free rate if monotherapy
→ residual struvite fragments can prevent urine sterilization & ↑'s risk of stone regrowth
→ may be indicated for small, non-struvite, staghorns
→ performed with ureteric stent placed prior
- 3) open surgery → reserved for unusual situations in which a staghorn stone is not expected to be removed by a reasonable number of PNL or SWL procedures
- 4) Nx → option for patient with poorly functioning kidney with staghorn

Which stones are most resistant to fragmentation by SWL?

- 1) **cystine (hardest stone)**
- 2) brushite (CaPO₄)
- 3) COM
- 4) struvite
- 5) COD (apatite)
- 6) uric acid

What renal anatomic factors should be considered in deciding Rx modality for stones?

- a) obstruction or stasis
- b) hydronephrosis
- c) UPJO
- d) calyceal diverticulum
- e) horseshoe kidney
- f) renal ectopia or fusion
- g) LP location

Which renal anatomic anomalies are associated with an increased risk of stone formation?

- 1) UPJO (more than just stasis)
- 2) calyceal diverticulum (mainly effect of stasis)
- 3) horseshoe kidney or other fusion anomalies (more than just stasis)
- 4) ectopic kidney
- 5) MSK (more than just stasis)

What evidence suggests that the etiology of stones in UPJO is not simply stasis?

- 1) 70% of UPJO patients with non-struvite stones had a metabolic abnormality
- 2) 60% of recurrent stones, in the non-struvite group, occurred in the contralateral kidney

What are the management options for a patient with UPJO and renal stones?

- 1) PNL + antegrade endopyelotomy } success rates ~75%
 } best overall approach
 → less morbidity + good efficacy
- 2) pyeloplasty + pyelolithotomy/stone extraction } success rates ~80-85%
 } lap pyeloplasty only if limited stone burden

What is a calyceal diverticulum?

- congenitally derived, **non-secretory, urothelium-lined** eventrations of the renal collecting system that are filled with urine
- usually has narrow-necked communication with renal pelvis } urine fills passively
- 0.5% incidence
- **10-50% are associated with stones** } **most will need intervention**

What are the management options for a patient with a CALYCEAL DIVERTICULAR stone?

→ goal is to prevent stone recurrence by eradicating diverticulum at time of stone removal

- 1) **PNL + ablation of diverticular urothelium + incision of narrow neck**
 - ~90% success rates
 - direct PNL into diverticulum is best
- 2) **URS + incision of narrow neck + ablation of urothelium**
 - ~75% success rates
 - good for UP and midpole diverticulum, stone burden <2cm, and short and accessible diverticular neck
- 3) **lap nephrotomy + marsupialization + ablation of urothelium + ablation of neck + stone removal**
 - reserved for those with thin overlying parenchyma, a large stone burden, & an anterior lesion not easily accessible by PNL
- 4) **partial nephrectomy**
 - high morbidity when more MIS is available
- 5) **SWL**
 - doesn't eradicate urothelium of diverticulum
 - only ~20-25% success rate

What is a horseshoe kidney?

- median fusion of metanephric tissue with entrapment of isthmus (by the IMA) during ascent
- associated malrotation → posterior calyces are more medial than usual
→ inferior pole is more anterior than usual
- associated anatomic features
 - UPJO
 - elongated renal pelvis
 - high inserting ureter
 - abnormal vasculature } vessels tend to enter anteriorly, except at isthmus
- 2/3 will have hydronephrosis, infection, or stones

What are the management options for those with a HORSESHOE KIDNEY & renal stones?

- 1) **PNL** } **stone-free rates ~80%**
 - } usually subcostal kidney, anteriorly entering vessels, and more medial posterior calyces make it ideal
 - } **UP access better** as LP is anterior and difficult to access
- 2) **SWL** } ~30% stone-free rates
 - } anomalous orientation of calyces makes stone localization difficult
 - } reserved for those with stone burden <1.5cm and no evidence of obstruction

What are the management options for ECTOPIC KIDNEYS with renal stones?

→ **pelvis is the most common location for an ectopic kidney**

- 1) **SWL** } **should be 1st line therapy**
 - } pelvic kidneys may be difficult due to bony pelvis so may need to do prone
- 2) **URS** } reserved for those with smaller stone burden
- 3) **CT-guided PNL**
- 4) **laparoscopic, transperitoneal PNL**
- 5) **laparoscopic, retroperitoneal pyelolithotomy**

What anatomic factors might make stone clearance from the LP less likely?

- gravity → dependent position
 - presence of multiple infundibula
 - narrow infundibulum (<5mm)
 - infundibulopelvic angle <90 degrees
 - longer infundibulum (>3cm)
- \ /
/ \ } poor drainage
/

What are the management options for LP stones?

→ **NOT CLEAR CUT**

- **depends on size** → SWL for stones <10mm
→ PNL for stones >20mm
→ SWL, PNL, or URS for 10-20mm
 - consider LP anatomy, stone composition for stones 10-20mm
 - PNL better but most morbid
- overall stone-free rate for SWL is ~60%, PNL stone-free rate is ~90%
- URS should be reserved for large stone burden that are poor candidates for PNL

What other techniques to facilitate passage of LP stones have been described?

- controlled inversion therapy +/- percussion
- retrograde irrigation of LP during SWL
- irrigation of LP via perc NT during SWL

Clinical Factors

What patient/clinical factors should be considered in deciding Rx modality for stones?

- a) UTI → PNL or URS preferred if complete stone removal needed (eg struvite stones)
 - risk of sepsis after SWL is <1%
 - SWL only after sterilization of urine + no distal obstruction
 - risk of sepsis is high
 - prophylactic Abx req'd only in high-risk patients
- b) morbid obesity → higher peri-op risk, difficulty targeting stone during SWL, wt limit of table/gantry, and skin-to-stone distance >max focal distance
 - PNL recommended for large stone burden
 - outcome of PNL is independent of BMI
 - URS preferred if stone burden not too large
- c) spinal deformity or limb contractures → positioning may be difficult within lithotripter
 - PNL or flexible URS may be preferred
 - pre-op CT to help plan PNL, may need CT guidance
- d) uncorrected coagulopathy → **URS + laser preferred for all w/ uncorrected coagulopathy**
- e) kids, elderly, HTN'sive, renal impaired pts → be careful with SWL
 - enhanced adverse effects of the shockwaves

Assessment and Management of Residual Fragments

Why is it difficult to compare most endourologic stone removal studies?

- 1) different methods of reporting treatment results
 - stone-free VS success rates (stone-free + clinically insignificant residual fragments)
- 2) lack of consensus regarding definition of clinically insignificant residual fragments
- 3) the use of different modalities to assess post-procedural stone-free status
 - KUB vs CT vs IVP vs U/S
 - KUB and IVP often over-estimate stone-free rates

What is the problem with “clinically insignificant residual fragments”?

→ **defined as residual fragments <4mm associated w/ sterile urine & asymptomatic patient**

- 1) can become symptomatic } 20-40%
- 2) can act as nidus for new stone growth } usually in LP, regardless of initial location
- 3) if struvite stone, may perpetuate post-op bacteriuria and persistent infection
- 4) if cystine stone, will shorten intervals between treatment

What follow-up imaging is recommended after stone removal procedures?

- SWL → KUB and/or U/S if asymptomatic } CT if symptomatic
- PNL → gold standard is flex. nephroscopy } NCCT may obviate routine flex. nephroscopy
 - KUB adequate for most } unless stone is radiolucent
 - antegrade nephrostogram
- URS → KUB (if radiopaque)
 - U/S or CT

Adjunctive Medical Treatment

What is the medical management of patients undergoing stone removal procedures?

- metabolic evaluation + stone analysis for all patients that require surgical stone removal
- selective medical Rx, regardless whether stone-free or residual fragments
 - significantly lower stone recurrence rates

- 1) available equipment
- 2) cost
- 3) surgeon's skill and expertise

What is the mechanism of ureteric colic?

→ **mediated by PGs released by obstructed ureter**

- 1) increases ureteral peristalsis (pain)
- 2) sensitizes nociceptors (pain) } bradykinins, C-fibers
- 3) induces visceral responses (nausea, vomiting)

→ **NSAIDs can help } decreases ipsilateral renal blood flow by ~1/3**

What is the most cost effective treatment of ureteric stones, after observation?

- URS → regardless of location (if done as outpatient)

How can you distinguish a phlebolith from a distal ureteric stone on CT?

- phlebolith } target sign (central lucency)
 } comet sign (curved vein attached to calcification)
- stone } rim sign (stone surrounded by edematous ureter)
 } hydronephrosis
 } ipsilateral renal enlargement
 } periureteral fat stranding

Proximal Ureteral Stones

What are the management options for PROXIMAL ureteral stones?

- 1) **SWL +/- manipulation** → **1st line option for stones <10mm**
 - reconsider if impacted, cystine, COM, obese, bleeding d/o
 - no clear benefit with stent placement
 - 75% stone-free rates
- 2) **URS** → **1st line option for stones of ANY SIZE (new from AUA Update)**
 - also if **stent req'd anyway, impacted, cystine, COM, bleeding d/o, distal obstruction, skeletal abN's, obese, pilots, pt preference, etc**
 - 75% stone-free rates \ with newer, better
 - complication rate now <1% / technology
- 3) **PNL** → reserved mainly for complex, large proximal ureteral stones
- 4) open or laparoscopic ureterolithotomy → salvage only

What are the indications for PNL to treat ureteric stones?

- large, complex proximal stones
- distal ureteric stricture
- urinary diversion
- concomitant renal stone
- failed URS or SWL

Distal Ureteral Stones

What are the management options for DISTAL ureteric stones?

→ **controversial**

- 1) **URS** → 90% stone-free rates \ pros and cons to
- 2) **SWL** → 85% stone-free rates / both modalities
- 3) blind basketing → NOT RECOMMENDED
- 4) open ureterolithotomy → NOT RECOMMENDED

What are the advantages & disadvantages to SWL & URS for distal ureteric stones?

	ADVANTAGES	DISADVANTAGES
SWL	<ul style="list-style-type: none">- effective- non-invasive w/ less morbidity- seldom need stents- less anesthetic req'd	<ul style="list-style-type: none">- slightly lower success rate- equipment not readily available- visualization of stone may be hard- stone-free state takes longer- higher re-treatment rates- more expensive
URS	<ul style="list-style-type: none">- very successful- minimally invasive- minimal morbidity- good for larger & multiple stones- immediate stone-free rates (less ancillary)	<ul style="list-style-type: none">- need more anesthesia- more often requires stent- specialized training needed

Laparoscopic Ureterolithotomy

What are the indications for laparoscopic ureterolithotomy?

- retroperitoneal vs transperitoneal approaches
- 1) concomitant upper tract abnormality needing repair } ureteral stricture, UPJO
- 2) salvage therapy after failed URS and SWL

STONES DURING PREGNANCY

What is the danger of renal colic in pregnancy?

- **most common cause of non-obstetric admission during pregnancy**
- **can cause PTL** } usually presents during T2 or T3
- symptomatic stones NOT more common during pregnancy
- N to have hydro during pregnancy } mechanical (uterus) + endocrine (progesterone)
} upper tract dilation seen in 90% by T3 } R >> L

What factors make a woman lithogenic during pregnancy?

- 1) hypercalciuria → increased GFR + filtered Ca
→ placental production of Vit D
- 2) hyperuricosuria → increased GFR + filtered uric acid
- 3) hyperoxaluria
- 4) increased UTIs
- 5) urinary stasis/dilation

What factors off-set the lithogenic factors seen during pregnancy?

- 1) increased urinary excretion of inhibitors → increased GFR + filtered citrate/Mg/nephrocalcin
- 2) increased urine output → increased RBF & GFR
- 3) increased urine pH

What is the role of imaging during pregnancy?

- embryo very sensitive to radiation during T1 → organogenesis
- during T2/T3 teratogenicity is less of an issue but risk of carcinogenesis & mutagenesis exists
- **no defined level of safe radiation** } ~5rads
- U/S is 1st line modality to assess for stones → low specificity and very low sensitivity
- limited IVP only if absolutely needed → scout, 30 sec, 20 min
- MRI → good because no radiation but hard to see stones

Exam	Total radiation dose (mSv)	Adult cancer deaths per 100,000
US	0	0
Nuclear scan	< 0.15 rads	
KUB	1.0 0.2 rads	5
IVP	3.0 < 1.5 rads (0.4-1.2)	15
CT Abdo	13.5	67.5
CT KUB 220 mAs	5.7	28.5
CT KUB 110 mAs	2.9	14.5
CT KUB 80 mAs	2.0	10
Environmental background	2.0/year	

How can one make U/S more sensitive for stones?

- 1) use colour-Doppler to identify ureteric jets and distinguish distal ureter from vessels
- 2) measure renal RIs → increases with acute obstruction (>0.7)
- 3) transvaginal U/S to assess distal ureter

What is the management of stones during pregnancy?

- **50-80% of stones will pass spontaneously with conservative management**
- about 1/3 need decompression for refractory pain, infection, etc
- NT recommended if early → will need to change stent frequently } q6-8 weeks
(≤22wks) → encrusts faster during pregnancy (heterogenous nucleation)
- URS during pregnancy is safe → don't use U/S lithotripters (?hearing injury to fetus)
→ minimize RADs by using below-the-patient xray & lead shield apron
- PNL not recommended during pregnancy → prolonged anesthesia + radiation exposure
- SWL contraindicated during pregnancy

STONE REMOVAL: TECHNIQUES AND TECHNOLOGY

Intracorporeal Lithotriptors

What are the different types of intracorporeal lithotriptors?

- 1) flexible → EHL
→ laser
- 2) rigid → ballistic (pneumatic)
→ ultrasound

How does EHL work?

- composed of 2 concentric electrodes of different voltage polarities
- when current overcomes insulated gap, a spark is produced } underwater “spark plug”
- **spark causes explosive formation of plasma channel + vaporization of surrounding H₂O**
- **expanding plasma causes hydraulic shockwave then formation of a cavitation bubble**
- shockwave is not focused (as with SWL) so the stone must be placed where it is generated
- probe placed 2-5mm distal to ureteroscope } 1mm from stone surface
→ **ONLY NON-CONTACT LITHOTRITRITE**

What are the advantages & disadvantages of EHL?

advantages	disadvantages
→ fragments 90% of stones	→ high risk of ureteral perforation (8%), especially at high energies and if stone is impacted
→ flexible, especially 1.6Fr probe	→ often associated w/ hemorrhage (poor vision)
→ cheap generator and probe	→ high rate of retropulsion
	→ forms larger number and sized fragments
	→ can cut basket & guide wires

How does laser lithotripsy work?

- “Light Amplification by Stimulated Emission of Radiation”
- **energy stimulates an atom to produce excited electrons, which releases light energy**
- **laser light is coherent (photons in phase), collimated (photons travel parallel), and monochromatic (photons have same wavelength)**
→ **transmission of []’d energy**
- laser named after the laser medium generating specific wavelength
- coumarin pulsed-dye laser } absorbed by all stones (except cystine) but not by tissue around (504nm) } takes 20min to get ready and is expensive
- **holmium:YAG laser } longer pulse duration produces elongated cavitation bubble (2140nm) that generates only a weak shockwave**
 - } **absorbed by water so little damage to surrounding tissue**
 - } zone of damage is **0.5 to 1.0mm**
 - } **photothermal mechanism causes stone vaporization**
 - } multiple laser fibers (200, 365, 550, 1000 micron)
- start at low setting and increase as needed (eg 0.2 J and 20 Hz)
- laser fiber placed in direct contact with stone → paint stone and don’t fragment or drill stone
- extend fiber tip 2mm from end of ureteroscope

What are the advantages & disadvantages of LASER?

advantages	disadvantages
→ safe and can be fired 1mm from wall (1% perforation rate)	→ expensive generator and laser fibers
→ flexible fibers (200, 365 micron)	→ produces cyanide when uric acid stones are fragmented (NOT CLINICALLY SIGNIFICANT)
→ effective for all stones (>95%)	→ slower
→ produces small fragments	→ can cut through basket and guide wires
→ low risk of retropulsion	
→ laser ready in 1 minute	
→ can also be used for strictures, BPH, TCC	

How does ballistic lithotripsy work?

- **relies on the energy generated by the movement of a projectile (“jack-hammer effect”)**
- compressed air (Lithoclast) or electromagnetic field (electrokinetic) is energy source

What are the advantages & disadvantages of ballistic lithotripsy?

advantages	disadvantages
→ effective for most stones (90%)	→ rigid
→ fast	→ produces large fragments
→ can pin down stones against urothelium	→ high rate of stone retropulsion
→ lowest risk of ureteral perforation (<1%)	
→ no heat generated so no thermal injury	
→ cheap	

How does ultrasonic lithotripsy work?

- **electrical energy vibrates piezoceramic plate which resonates at a specific frequency and generates ultrasonic waves (23,000 to 25,000 Hz)**
- **ultrasound energy is transformed into vibrational energy via hollow steel probe**
 - small 2.5 French probe is solid
- **probe tip causes stone to resonant at high frequency and to break**
- soft tissue doesn't resonate and so isn't damaged
- connected to suction, which allows removal of debris
 - if suction pressures are too high, air bubbles can be drawn into system (poor vision)
- excellent for PNL → pin stone between probe and urothelium and apply gentle pressure

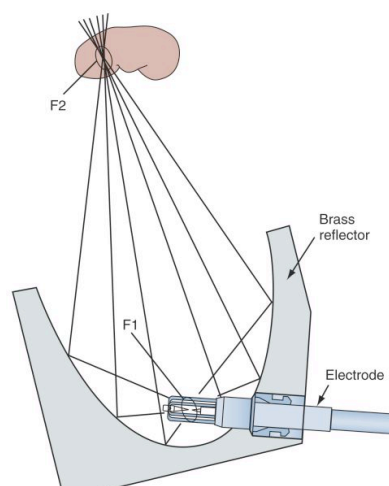
What are the advantages & disadvantages of ultrasonic lithotripsy?

advantages	disadvantages
→ effective for most stones <ul style="list-style-type: none">- cystine, COM, uric acid stones relatively resistant	→ rigid
→ can fragment AND remove fragments simultaneously	→ large probes (2.5 –12 French)
→ fast	→ risk of perforation can be high if too much pressure is applied to the urothelium
→ limited heat generated so very minimal thermal injury	

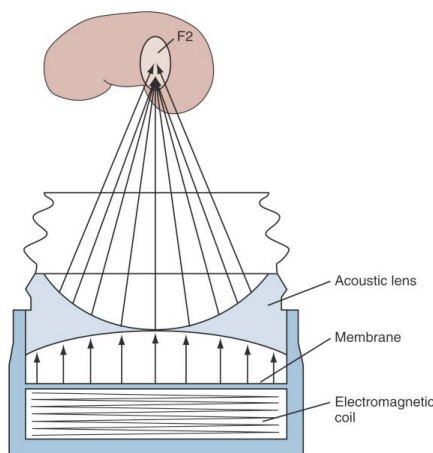
Extracorporeal Shockwave Lithotripsy

What are the different types of SWL generators?

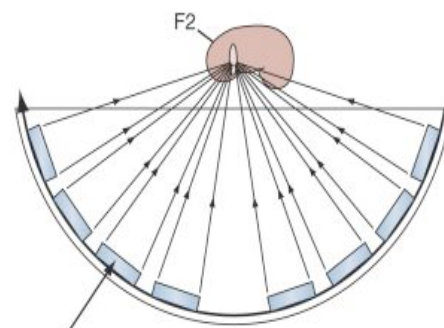
- 1) electrohydraulic (spark gap) → spherically expanding **shockwave is generated by an underwater spark discharge**
 - **electrode at F1 and stone at F2**
 - reflector focuses shockwave energy at F2
 - **eg Dornier HM3, HealthTronics Lithotron Ultra**
- 2) electromagnetic → plane or cylindrical **shockwaves generated by magnetic field** created between electromagnetic coil conductors
 - **only F2** } acoustic lens (plane) or parabolic reflector (cylindrical) used to focus shockwave energy at F2
 - eg Siemens Lithostar, Dornier DoLi
- 3) piezoelectric → plane **shockwaves generated by rapid expansion of ceramic elements**
 - **only F2** } crystals are oriented in a spherical dish that focuses energy at F2
 - eg Wolf P3000
- 4) other → microexplosive lead azide generator
 - laser beam generator
 - multi-stage light gas gun generator



→ ELECTROHYDRAULIC



→ ELECTROMAGNETIC



→ PIEZOELECTRIC

What are the advantages & disadvantages of each of the different SWL generators?

	ADVANTAGES	DISADVANTAGES
electrohydraulic	<ul style="list-style-type: none"> - effective at breaking stone - low rate of subcapsular hematoma (<1%) 	<ul style="list-style-type: none"> - short electrode life - fluctuations in pressure with each shock
electromagnetic	<ul style="list-style-type: none"> - less painful because energy introduced over larger area - more controllable and reproducible - effective at breaking stones - long electrode life 	<ul style="list-style-type: none"> - high rate of subcapsular hematoma from small focal region of high energy (5-10%)
piezoelectric	<ul style="list-style-type: none"> - accurate focusing - little pain due to large area of entry - long ceramic life 	<ul style="list-style-type: none"> - less effective at breaking stone

What are the different methods of stone localization?

1) U/S alone → advantages

- cheap and low maintenance
- no radiation
- can see radiopaque AND radiolucent stones

→ disadvantages

- needs skilled operator
- hard to see stones in midureter and in the presence of a stent

2) fluoroscopy alone → eg Dornier HM3

→ advantages

- easy to use
- can see radiopaque stones throughout collecting system
- can use contrast to help localize radiolucent stone
- can display anatomic detail

→ disadvantages

- radiation exposure
- high maintenance
- can't see radiolucent stones without dye

3) U/S + fluoro → eg Lithotron Ultra (U/S optional)

What causes pain during SWL?

- related directly to the energy density of shockwaves as it passes through skin
- relates to size of F2

What different types of anesthesia are used during SWL?

- GA → better stone-free rates } ?more controlled respiratory excursion
- neurolept → versed + propofol } adequate for most
- EMLA cream → topical lidocaine + prilocaine } decreases amount of neurolept needed

Which lithotripter is the best?

- unmodified Dornier HM3 (original SWL generator) is the most effective
- no studies to show Dornier HM3 has more adverse effects
- water bath is best way of transmitting shockwave energy

How are stones fragmented?

- stone breaks due to **mechanical stresses produced either directly by incident shockwave or indirectly by collapse of cavitation bubble**
- initial short, steep compressive pressure front (~40 MPa) which is followed by longer, lower amplitude negative (tensile) pressure (10MPa) } entire pulse lasts 4 μs

Name 6 theories behind stone fragmentation. } } } “SSS CAD”

- 1) Spall fracture → shockwave enters then hits sites of impedance mismatch (eg distal surface), reflecting back, creating tensile (negative) wave that fractures stone
- 2) Superfocusing → shockwaves going through stone bounce off different internal aspects of stone and may focus energy at a point and form very high stress
- 3) Shear stress → shockwave passes through stone & causes transverse waves, resulting in areas of high shear stress
- 4) Compression (squeezing-splitting) → shockwave passes faster through stone than surrounding fluid, causing circumferential compression force
- 5) Acoustic cavitation → collapse of cavitation bubble causes increased pressures on stone
- 6) Dynamic fracture → accumulated damage by tensile and/or shear stress leads to fragmentation

What are the contraindications to SWL?

- absolute } } } “Habitual COUCH Potato”
 - 1) **H**abitus (obesity, orthopedic deformities)
 - 2) **C**oagulopathy
 - 3) **O**bstruction distally
 - 4) **U**TI
 - 5) **C**alcified renal artery aneurysm or AAA
 - 6) **H**TN uncontrolled
 - 7) **P**regnancy
- relative
 - 8) large stone burden
 - 9) certain stone types } cystine, COM, matrix
 - 10) certain anatomic features } horseshoe kidney, calyceal tic, ectopic kidney
- **KIDS can get SWL, but cover lungs to avoid contusion**
- **BILATERAL can be done, but should probably stent at least one side**

What are the predictors of SWL failure?

- ~80% of all patients with “simple” stones will be treated successfully by SWL
- 1) large stone size
- 2) stones in LP
- 3) stones in obstructed portion of kidney
- 4) stone composition } cystine, CaPO₄ (brushite), COM (whewellite)
- 5) obesity
- 6) unsatisfactory targeting of the stone

List indications for stenting prior to SWL } } } “SORRI, Stent Patient Before”

→ consider ureteroscopy in some cases where pre-SWL stent is indicated

- Solitary functioning kidney
- Obstruction prior to stone
- Renal colic (refractory)
- Renal insufficiency
- Infection with obstruction
- Size >1.5cm
- Poorly visualized stone
- Bilateral SWL

Which stone types are the most resistant to SWL?

- 1) cystine \
 - 2) CaPO₄ (brushite) }
 - 3) COM /
 - 4) struvite
 - 5) hydroxyapatite
 - 6) Ca oxalate dihydrate
 - 7) uric acid
- } these stones should only be treated with SWL if <1.5cm
→ PNL or URS recommended

What other factors of stone composition can help predict SWL success?

- smooth, round, homogeneous stones → harder to fragment
- stone density/attenuation values → more dense stones harder to fragment

What are the potential complications of SWL?

1) acute extra-renal damage

- liver trauma
- skeletal muscle trauma
- gastric and duodenal erosion
- lung parenchymal injury
- pancreatitis } both symptomatic and asymptomatic
- colonic trauma } hematochezia
- cardiac arrhythmias } rare; ? reduced with increasing rate of SWL or gating SWL
→ higher rate decreases efficiency of stone fragmentation

2) acute renal injury

- subcapsular hematoma (newer generation 5-10%)
 - more common in elderly & with electromagnetic generators
 - may need transfusions & embolization
 - usually takes 6weeks to resolve
- hematuria
- intrarenal & perinephric edema } usually resolves within a few days
- injury to nephrons and small to medium-sized vessels at F2 (always occurs)
 - vasoconstrictive response } increased with increased shockwaves
- acute renal failure } decreased intrarenal blood flow & GFR (one of main causes)
- delayed excretion of contrast
- elevated RIs, particularly in elderly } assoc'd w/ new HTN (indicative of underlying disease)
- Steinstrasse (5-10%)
- UTIs/pyelonephritis (5-10%)
- renal colic requiring admission
- failed lithotripsy

3) chronic renal injury

- accelerated rise in BP } not clear if directly causes HT
(mainly DBP) } occurs more in elderly → ?underlying disease
} some have shown no difference b/w URS, PNL, observation
- decrease in renal function
- increased stone recurrence rate } residual stone debris
- more brushite stones
- ??? DM

What are the RFs for acute renal injury after SWL (CHART)?

- 1) age } kids and the elderly
- 2) obesity
- 3) coagulopathies
- 4) thrombocytopenia
- 5) DM
- 6) CAD
- 7) pre-existing HTN } highest rate of perinephric hematoma

What are the renal side effects of SWL seen in animal models (CHART)?

- 1) acute histologic changes
 - } venous thrombi
 - } cellular disruption and necrosis
 - } mild tubular necrosis (ischemic changes)
 - } intraparenchymal hemorrhage
 - } tubular dilation and cast formation
 - } damage and rupture of veins and small arteries
 - } rupture of glomerular and peritubular capillaries
 - } increased free radical formation
- 2) chronic histologic changes
 - } nephron loss
 - } dilated veins (occurs after acute vasoconstriction)
 - } streaky fibrosis
 - } diffuse interstitial fibrosis
 - } Ca and hemosiderin deposits
 - } hyalinized and acellular scars from cortex to medulla

List factors that affect degree of renal trauma after SWL in animals (CHART)

- 1) increased # of shockwaves
 - 2) increased shockwave rate
 - 3) higher power settings
 - 4) treating a juvenile kidney → smaller kidneys do worse
 - 5) treating impaired kidney (CRF, pyelo)
 - 6) type of extracorporeal lithotripter
- pretreating with 100-500 shocks at low energy levels (12kV) has been shown to decrease renal trauma and size of lesion/scar at F2

What are the reversible & irreversible acute changes in the kidney after SWL (CHART)?

- 1) reversible } mild tubular necrosis
 } casts and RBCs in tubular lumen
 } vacuolar changes of tubular lumen
 } mild interstitial edema and hemorrhage
- 2) irreversible } disruption of nephrons
 } extensive interstitial edema
 } large hematomas of cortex and medulla
 } rupture and occlusion of veins and arteries
 } fracture of glomerular and peritubular capillaries

**clinical dose of SWL
always induces some
irreversible injury**

What is the mechanism of renal tissue injury after SWL?

- collapse of cavitation bubbles
- causes rupture of blood vessels
- pooled blood potentiates cavitation bubble growth and collapse

PNL

What are the indications for percutaneous nephrostomy?

- 1) stone disease } eg staghorn
- 2) obstruction } eg UPJ obstruction
- 3) malignant or benign tumours } eg upper tract TCC
 } eg fibroepithelial polyps
- 4) infection } eg pyelo + obstruction

What are the absolute contraindications to PNL?

- 1) uncorrected coagulopathy
- 2) active, untreated UTI
- 3) abnormal anatomy that precludes access (eg retrorenal colon)

What is involved in the pre-op evaluation prior to PNL?

- 1) Hx and P/E
 - r/o contraindications
- 2) investigations
 - CBC, lytes, BUN, creat, PTT, INR, group&screen
 - **urine culture (MANDATORY)**
- 3) imaging
 - CT } stone burden, planning, r/o retrorenal colon
 - KUB } immediate pre-op
 - IVP or retrograde if calyceal diverticulum suspected
 - renal scan } to evaluate differential function as Nx may be mgt of choice
- 4) antibiotics
 - 2 weeks of ABx for those suspected of struvite stone, presence of UTI
 - even if urine culture is -ve, colonized stent can release endotoxin w/ fragmentation
 - prophylactic Abx for all others
 - gram +ve coverage eg ampicillin (*S.epidermidis* most common secondarily infecting organism)
 - add gram -ve coverage for high-risk patients eg gentamicin

What type of anesthesia is required for PNL?

- 1) GA → best method } esp. for length PNL & upper pole access (can control respirations)
- 2) local → poor control of pain
→ no control of patient movement
- 3) regional/epidural → need very high block } airway protection issue
→ renal pelvis distension may induce vasovagal reaction

What are the benefits of placing a ureteral catheter?

- 1) can opacify and distend collecting system to make access easier
 - contrast is heavier so may fill anterior calyces
 - can add air bubbles to delineate posterior calyces (use <20cc) } reports of air emboli
- 2) minimize passage of stone fragments into ureter
- 3) allows retrograde irrigation
- 4) can instill contrast during procedure

What is the best way to obtain percutaneous access?

- 1) single stage → access + dilation + lithotripsy
→ antegrade vs retrograde
 - 2) 2 stage PNL can also be performed via IR
 - U/S guided perc access
 - fluoro-guided perc access after iv contrast
 - blind passage of Chiba needle (1.5cm lateral to transverse process at L1-L2 level)
- ➔ **direct puncture onto stone best for calyceal tic stone or difficult to access locations**

How do you position the patient for a PNL?

- [illegible]

What are methods to decrease radiation exposure?

- grid-controlled fluoro
 - aim more midline (less scatter)
 - use of last-image-hold function
 - collimation (narrows beam and thus less scatter)
 - place fluoro head/beam under table (less leakage and scatter)
 - use lead aprons & thyroid shields
 - use dosimeters to monitor exposure
- } scatter is main source of radiation to the endourologist

What are the anatomic considerations when obtaining percutaneous access?

→ usually antegrade but can be done retrogradely also

→ ideally **through Brodel's line** b/w anterior & posterior divisions of the main renal artery

- going through posterior calyx takes you through Brodel's line
- going through **posterior calyx** makes it easier to pass a guidewire into ureter
- occasionally anterior calyx is more optimal } middle calyces are less variable; polar regions more variable (compound)
- } anterior calyces are more lateral

→ access collecting system **along axis of calyx, through papilla, parallel to the infundibulum**

- avoid blood vessels adjacent to infundibulum
- less torque needed

→ **avoid direct infundibular access or direct puncture of the renal pelvis**

- high risk of vascular injury
- potential prolonged urine leak
- NT easily dislodged

[illegible]

→ access should be attempted during **expiratory phase** } lower risk of pleural complications

What are the considerations when choosing a calyx for PNL access?

➔ goal is to pick calyx that allows greatest removal of stone burden w/ rigid nephroscope

- LP, posterior calyx preferred when possible → less complications
- if solitary calyceal stone, access directly into the calyx preferred
 - for anterior calyceal stone, flexible nephroscope may be req'd as direct access is tough

What are the usual indications for supracostal puncture?

- 1) most of stone is in upper calyces
 - 2) associated UPJO that needs endopyelotomy
 - 3) multiple LP calyces with stones
 - 4) associated ureteral stone
 - 5) staghorn stone with substantial UP burden
- ~15% overall pleural complication rate
→ <5% required treatment

When should multiple percutaneous accesses be considered?

- 1) when any calyx, which is unreachable via the primary track, contains a stone >2cm
- 2) stones <2cm but they are not reachable with flexible nephroscope via the primary track

What are the RFs for the presence of a retrorenal colon?

→ <1% of patients have a retrorenal colon (in prone position)

→ more common near LP and on the L

- hx of jejunioileal bypass
- hx of renal surgery
- elderly (NH) patients
- patients with SCI
- very thin patients (females)
- ectopic/horseshoe kidneys
- dysmorphic body habitus from congenital malformations

What are the indications for a non-dilated puncture during PNL?

- to guide flexible nephroscope towards a difficult to locate calyx
→ methylene blue, CO2 bubbles, guidewire
- for insertion of a NT into a LP calyx when the primary access track is through an UP calyx
→ less post-op pain cf supracostal NT

How does one gain access once the calyx of choice has been decided?

- 18gauge needle directed into calyx under fluoroscopy
- adjustments made using C-arm → once renal parenchyma entered, it's hard to make adjustments as movement of needle also moves calyx
- aspirate urine to confirm position
- pass hydrophilic guidewire into collecting system } ideally into ureter, otherwise curl in renal pelvis
- if LP access used, can use Cobra catheter to direct guidewire through UPJ
- 8-10Fr coaxial dilators used to dilate track
- safety guidewire placed through double lumen catheter
- track dilated up to allow placement of working sheath } balloon dilators → expensive but fast and safe
} semirigid Amplatz dilators
} metal telescoping dilators
- can create open, low pressure system via working sheath or closed, high pressure system with nephroscope serving as its own sheath
→ open system preferred because } less risk of significant fluid absorption
} less risk of large-volume fluid extravasation
} easier insertion and removal of scopes
} can remove larger stones

How are stones removed once a working sheath is in place?

- warm NS used as irrigant → decreases risk of hypoNa in case of large-volume extravasation
- irrigant at ≤80cm to decrease intrapelvic pressure and to prevent absorption (pyelovenous)
- rigid nephroscope used first, followed by flexible nephroscopy to look for residual stones
- can grasp stones <1cm and extract via working sheath } can also use stone basket
- different intracorporeal lithotriptors can be used to remove stones

What are the complications of percutaneous renal surgery?

→ access-related

- bowel injury (colon, duodenum, pancreas) } <1%
- injury to liver or spleen
- pneumothorax/hemothorax
- hemorrhage
- lung injury
- positioning injury (nerve palsy, etc)

→ procedure-related

- hemorrhage
- renal pelvic injury
- ureteric injury
- extravasation
- fluid absorption } mainly if perf or venous injury (can get TUR syndrome)
- pleural effusion
- unable to find stone OR loss of stone through perf
- incomplete lithotripsy
- sepsis (1-2%)
- renal AVF

List potential complications of percutaneous renal surgery?

→ **minor complications in 10-25% and major complications in ~5%**

→ **8% complication rate for direct UP puncture**

- 1) hemorrhage → conservative mgt sufficient for most cases
 - <1% need angio + embolization } 40% AVFs, 35% pseudoaneurysms
 - for tract bleeding can use large-bore NT or Kaye catheter (tamponading)
 - council balloon catheter can be used for venous bleeding
 - **delayed bleeding almost always due to AVF or pseudoaneurysm**
 - 3-23% transfusion rate
- 2) injury to renal pelvis → usually due to aggressive passage of dilators or lithotripter
 - should stop PNL and place ureteral stent + NT
- 3) fluid absorption/volume overload → can occur if perforation or venous injury (“TUR syndrome”)
- 4) pulmonary complications → highest risk with intercostal approach between 10th and 11th ribs
 - small effusions seen intra-op may be tapped, large effusions, hemothorax, or pneumothorax may require a chest tube
 - pleural effusion/hydrothorax in ~8%, pneumothorax in 4%
 - post-op CXR for all intercostal PNLs
- 5) bowel injury → <1% of cases
 - more common in thin F, abN renal anatomy (horseshoe, ectopic), NH patients, previous jejunoileal surgery, previous renal surgery, anterior calyceal puncture
 - place stent then pull back NT and use as colostomy tube for extraperitoneal perf
 - ABx
 - imaging in 1wk + removal of perc tube if no communication with GU tract
 - laparotomy for intraperitoneal injuries or the presence of peritonitis/sepsis
- 6) injury to liver or spleen → rare unless hepatosplenomegaly } get CT-guided access
 - splenic injuries usually require laparotomy +/- splenectomy
 - liver injuries can usually be managed conservatively
- 7) sepsis → occurs in ~1-2% of cases
- 8) failed access in <5%
- 9) ureteral stone

What are the RFs associated with an increased risk of bleeding during percutaneous renal surgery?

- excessively medial puncture
- multiple punctures
- abnormal renal anatomy
- bleeding diathesis

What is the management of hemorrhage during/after PNL?

- usually venous
- NT placement } clamp NT to facilitate tamponade
- placement of a Kaye NT → balloon tamponade
- angio → r/o AVF or false aneurysm
- partial Nx → on the very rare occasion bleeding can't be controlled with angio

What is the management of extravasation of fluid?

- extraperitoneal → often see medial displacement of kidney
 - rarely enough to stop procedure but if significant perf, stop and place NT
- intraperitoneal → rare but can lead to more serious complications
 - may see rise in dBP, raised CVP, difficulty with ventilation
 - stop and aggressively diurese
- intrapleural → rarely occurs due to access sheath

What are the signs of colon perforation during PNL?

- intraop hematochezia or diarrhea
- peritonitis
- sepsis
- gas or feces drainage from NT
- contrast in colon during post-op nephrostogram

What is the management of a colonic injury?

- rare and usually retroperitoneal
- ureteral stent placed
- pull back NT into colon } serves as colostomy tube
 - left in situ for minimum 1 week
 - } remove after imaging in 1wk shows no communication with colon
- Abx
- NPO } consider TPN
- laparotomy if obviously intraperitoneal, sepsis, peritonitis, failure of conservative management

What are the indications for the placement of post-percutaneous drainage devices?

→ tubeless perc. surgery has been reported and seems safe & feasible in SELECT PATIENTS

→ **post-op drainage is the standard of care**

→ type of drainage device depends on:

- complicated vs uncomplicated procedure
- degree of bleeding
- likelihood of obstructing edema
- likelihood of repeat intervention
- patient tolerability
- endourologist's preference

What are the benefits of leaving a NT post-PNL?

- 1) tamponade bleeding from track
- 2) allow renal puncture to heal
- 3) allow proper drainage of urine
- 4) allow access to collecting system if secondary PNL needed

What are the indications for a tubeless PNL?

→ controversial } most cases described had ureteral stent placed (requires 2nd procedure)

- no residual stone burden
- short PNL
- single access only
- no perforation of collection system
- no significant bleeding

What are the different types of NTs used post-PNL?

- 1) Hobbs (NUT)
- 2) NT (pigtail, Cope loop)
- 3) red rubber
- 4) malecot
- 5) U-loop NT → for multiple access PNL
- 6) re-entry catheter (nephrostomy-stent)

What is the post-op course after PNL?

- KUB or antegrade nephrostogram 24-48hours after PNL
- clamp or remove if no stones and good drainage

PNL in Special Situations

What are the indications to treat a calyceal diverticulum?

- pain
- hematuria
- progressive renal damage
- recurrent UTIs
- symptomatic stones

How often are calyceal diverticula associated with stones?

- ~20 %

Why is PNL access into a calyceal diverticulum difficult?

- small size of cavity
- usually UP location
- can be hard to pass guidewire into renal pelvis
 - stone fills entire diverticulum
 - infundibular stenosis

What are the management options for calyceal diverticulum +/- stones?

- goal is to prevent stone recurrence by eradicating diverticulum at time of stone removal
- 1) **PNL + ablation of diverticular urothelium + incision of narrow neck**
 - ~90% success rates for stones
 - direct PNL into diverticulum is best
- 2) **URS + incision of narrow neck + ablation of urothelium**
 - ~75% success rates
 - good for UP and midpole diverticulum, stone burden <2cm, and short and accessible diverticular neck
- 3) lap nephrotomy + marsupialization + ablation of urothelium + ablation of neck + stone removal
 - reserved for those with thin overlying parenchyma, a large stone burden, & an anterior lesion not easily accessible by PNL
- 4) partial nephrectomy
 - high morbidity when more MIS is available
- 5) SWL
 - doesn't eradicate urothelium of diverticulum
 - only ~20-25% success rate

Why is direct puncture into the diverticulum preferred for calyceal diverticular stones?

- allows use of rigid instruments which provide better visualization
- better visualization needed to identify communication into renal pelvis
- allows fulguration of urothelium using a resectoscope

How is PNL for a calyceal diverticular stone performed?

- puncture diverticulum and place working and safety guidewires → coaxial dilators
- balloon dilator used and working sheath advanced almost into diverticulum
 - for large diverticulum, sheath can be advanced into diverticulum
- alligator forceps used through nephroscope to gently spread renal parenchyma and access diverticulum under direct vision
- stone removed with forceps, basket, lithotripter
- carefully examine urothelium to r/o a flattened renal papilla
 - evidence that it's an obstructed calyx rather than a diverticulum
- identify neck of diverticulum → may need methylene blue via ureteral occlusion catheter
- pass guidewire into renal pelvis → dilate or incise neck of diverticulum
- +/- fulguration of calyceal diverticular urothelium
- placement of NT or NUT → 72hrs to 2 weeks

Why is ureteral obstruction common in horseshoe kidneys?

- 1) high insertion of ureter into typically elongated renal pelvis
 - 2) aberrant course of proximal ureter → drapes ventrally over renal symphysis where it can be compressed by vessels to lower pole & isthmus
- stones seen in up to 70% of patients

What are the special considerations for PNL access in horseshoe kidneys?

- lower & centrally located kidney → slightly higher risk of retrorenal colon
- abN orientated collecting system → LP calyces not suitable for direct puncture b/c medially angled
→ UP better b/c more posterior & lateral, as well as being subcostal
→ almost always will need flexible nephroscope
- abN blood supply → puncture from dorsal or dorsolateral aspect will keep away from ventromedially inserting aberrant and accessory vessels

What are the RFs for stone formation in a transplanted kidney?

- rare (<3%)
- presentation not typical because kidney & ureter denervated } no renal colic & like rejection or ATN
- 1) metabolic abnormalities } hypercalciuria, hyperCa, hyperoxaluria
- 2) foreign bodies (nonabsorbable sutures, retained stent)
- 3) recurrent infection
- 4) papillary necrosis

What are the special considerations for PNL access in a **transplanted kidney**?

- if L kidney placed in R iliac fossa, or vice versa, renal pelvis will be medial and anterior
→ posterior calyces will be pointing anterior
- superficially located transplanted kidney facilitates PNL, but scar around kidney may make puncture and track dilatation harder (dilated tracks heal normally in most)
- access into LP calyces safest to avoid intraperitoneal contents

What are the special considerations for PNL access in an **ectopic/pelvic kidney**?

- kidney is anterior to sacrum and posterior to peritoneal contents making direct access hard
- reports of **lap assisted PNL**
- **CT guided percutaneous access**

What are the special considerations in performing PNL in the morbidly obese patient?

- **outcome of PNL is independent of patient's BMI**
- anesthesia → higher vent pressures needed due to restricted lung capacities in prone patient
- imaging → wt may prevent assessment of stone location, stone burden, & skin-stone distance
- positioning → table weight capacity, table size
- access → long skin-to-stone distance } need extra-long working sheaths, nephroscopes

What techniques can be used to deal with the long skin-to-stone distances in obese patients?

- use of extra-long equipment
- incision made through subcutaneous tissue and PNL track started at level of muscles
- dilate and mature track for 1 week prior to PNL with NT
- liberal use of flexible nephroscopes
- post-PNL NT displacement more common in obese pts } consider malecot or balloon-type catheter
} consider ureteral stent + Cope loop NT

What is the role of simultaneous bilateral PNL?

- safe, less morbid, more rapid method of stone resolution
- better if combined with epidural
- always start with more symptomatic or more difficult side first
- proceed with 2nd side if } no significant bleeding on first side
} first side didn't take too long
} patient is stable
} anesthesia is happy to proceed

Ureteroscopic Management of Ureteral Stones

What are the indications for ureteroscopy (CHART)?

- 1) Diagnostic
 - evaluation for +ve cytology with normal cysto
 - monitoring of previous upper tract TCC
 - evaluation of filling defects on IVP or retrograde
 - undiagnosed gross hematuria
- 2) Therapeutic
 - stones
 - ureteral stricture
 - retrograde endopyelotomy for UPJ obstruction
 - biopsy or ablation of upper tract TCC
 - retrieval of migrated stent or other FB

What are the indications for ureteral dilation?

- rarely required with new smaller ureteroscopes
- inability to pass ureteroscope (<15%)

What are the benefits of ureteroscopy using an access sheath?

- shorter OR times
- higher stone-free rates
- easier ureteral re-entry
- less damage to ureteroscope
- lower intrapelvic pressures
- can dilate narrow ureteric orifice

What are the indications to leave a stent after URS? } } } “I Like Inserting Stent For Difficult Procedures”

- 1) **Infected + obstructed urinary system**
- 2) **Large stone burden with lots of fragments left to pass**
- 3) **Impacted stone causing significant ureteral edema**
- 4) **Solitary kidney**
- 5) **Failure to advance ureteroscope due to narrow ureter/UO } in preparation for repeat URS in ~1wk**
- 6) **Dilation of ureter >10Fr (coaxial or balloon)**
- 7) **Perforation intra-op**
 - to prevent renal colic from stones or edema
 - to facilitate stone passage
 - to prevent stricture formation

How successful is URS for stones?

- distal ureteric stone → >95% stone-free rate (better than SWL 85%)
 - less OR time, fluoro time & earlier stone-free status
- proximal stones → >90% stone-free rate (better than SWL 70%)
 - SWL 1st line for stones <1cm
 - if >1cm, SWL, URS and PNL are all equally viable options
- renal stones → 85-90% stone-free rates
 - ok for stones <2cm, otherwise PNL better
 - LP stones have worse outcomes

List the indications for URS over SWL for ureteric stones } “DR, SCOOP Fast Man”

- **Dense stone (cystine or COM or brushite)**
- **Radiolucent stones**
- **Size >1cm**
- **Coagulopathy (uncorrected)**
- **Obese (morbid)**
- **Occupation → pilots must be stone-free**
- **Patient preference**
- **Failed SWL**
- **Multiple proximal ureteric stones**

What are the complications of URS?

- 1) intraop
 - failure to access ureter, kidney, stone
 - failure to fragment stone
 - stone migration into ureteral wall
 - mucosal trauma
 - ureteral perforation → <5% } treated with indwelling stent
 } upper ureter more susceptible (thinner muscularis)
 - ureteral avulsion → usually occurs during basketing } telescoping + avulsion
 → requires open surgery (UU, reimplant, ileal interposition, autoTx, or Nx)
- 2) early post-op
 - gross hematuria
 - renal colic (stone fragments, clot, ureteral edema)
 - large residual stone fragments needing ancillary procedure
 - pyelonephritis/urosepsis
 - urinoma
 - ureteral stent symptoms
- 3) late post-op
 - ureteral stricture → 4-5%
 - retained encrusted stent

What are the complications of ureteral stone management?

- **with modern ureteroscopes, overall complication rates are <1%**
- **most complications that occur can be managed with ureteric stent placement**
- 1) perforation → decreasing due to smaller flexible scopes and better lithotrites
 - most common with EHL lithotrite
 - significant risk of developing strictures
 - Rx → stent x2-4weeks + careful radiographic f/u
- 2) stricture → mainly from:
 - a) impacted stone } higher rate of stricture formation with increasing duration of impaction
 - b) ureteral perforation } stent placement for 2-4weeks may decrease chance of stricture formation
 Rx → includes incision (cold knife, laser, etc) or balloon dilation + stent
- 3) submucosal stone → iatrogenically displaced submucosal stones are difficult to remove, and ureteral perforation with urinoma can occur
 - intense fibrosis often develops
 - Rx → laser excision + stent placement
 - open resection may be required if laser excision fails
- 4) lost stone → stone outside ureter doesn't usually need further treatment
 - perforation may cause stricture formation
 - if struvite stone, then may form retroperitoneal abscess
- 5) avulsion → most severe complication
 - usually requires open repair } may attempt to place stent for several months if guidewire already in place

What are the RFs for ureteral perforation during/after ureteroscopy?

- 1) long OR time
- 2) use of EHL
- 3) impacted stone
- 4) renal stones
- 5) surgeon inexperience

What are the common causes of ureteral strictures?

- idiopathic
- acquired
 - malignancy → TCC, metastatic cancer (eg cervical, prostate, etc)
 - TCC classically presents as goblet sign filling defect but can present as stricture
 - ureteral stone (impacted)
 - RADs
 - ischemia/trauma from surgical dissection
 - periureteral fibrosis from AAA or endometriosis
 - endoscopic instrumentation
 - infection (eg TB, schisto)

What are the predictors of successful endourologic treatment of strictures?

- ischemic vs non-ischemic → ischemic strictures do poorly
- length → <2cm do better
- urine flow through area of incision → necessary for successful endourologic treatment
- poor renal function → if <25% of total renal function, more likely to fail

What are the RFs for steinstrasse?

- 1) large stone burden } occurs more frequently with increasing stone size
 - 2) staghorn stones
 - 3) bilateral SWL
 - 4) pre-existing ureteral obstruction
- occurs in 2-10% of SWL cases } 70% occurs in distal ureter

What is the management of steinstrasse?

- stent placement prior to SWL decreases steinstrasse & sequelae in some studies
- other studies have shown no benefit in stent placement prior to SWL, regardless of stone size
- **if asymptomatic, observe** } ~70% will resolve & clear stones spontaneously
 - } should use Abx & repeat U/S
- placement of a NT may allow passage of stones in up to 75% of patients
- **URS is treatment of choice**

What are the indications for intervention in a patient with steinstrasse?

- 1) refractory pain
 - 2) bilateral obstruction
 - 3) obstruction in a solitary kidney
 - 4) associated with infected hydronephrosis
 - 5) large leading fragment unlikely to pass
 - 6) failure of expectant management
 - 7) renal insufficiency/failure
- URS is 1st line management
- repeat SWL of lead fragment less successful
- PNL should be reserved as a salvage procedure for upper ureteric steinstrasse
- open surgery should be reserved for failure of other methods or for complications

What are the indications for ureteroscopic management of renal stones?

- failed SWL
- radiolucent stones
- concomitant ureteral & renal stones
- renal stones associated with intrarenal stenosis
- nephrocalcinosis or urinary diversion
- patients with the need for complete stone removal (eg pilots)
- bleeding disorders
- morbid obesity

- mean overall success of a single session is ~85% } complete clearance or insignificant residual fragments
- residual fragments associated with:
 - increasing size and number of stones
 - LP location
- should not be used for staghorn stones
 - not an appropriate alternative to PNL unless PNL contraindicated

- no need for pre-op stent in most cases } new smaller scopes
- } ureteral dilation required in <10%
- ureteral access sheath may facilitate stone removal for cases of multiple stones or large stone burden requiring multiple passages of a basket
- place 2 guidewires → safety and working
- monorail flexible ureteroscope over working guidewire
- place patient in Trendelenburg } fragments fall into upper pole
- goal is to break stones into dust and small fragments <2mm
- if lower pole stones are difficult to laser, can move them into renal pelvis

What are the indications to consider laparoscopic lithotomy?

- 1) pyeloplasty with pyelolithotomy
- 2) stones in poorly functioning polar areas or with nonfunctioning kidneys
- 3) pelvic kidneys with large stone volume → reflect overlying bowel to allow PNL
- 4) ureterolithotomy for extremely rare endoscopic failure

What are the indications for open renal stone surgery?

- slightly higher stone-free rates than PNL alone, but similar to PNL + SWL
- should only be for patients refractory to multiple PNL, SWL, ureteroscopy } SALVAGE
- Nx should be an option for those with huge staghorns and a non-functioning kidney

- as a salvage procedure when a planned abdominal procedure coincides with a symptomatic ureteral stone
- when another ureteral abnormality requiring open surgical repair coincides with a stone

Describe how to do a lower ureterolithotomy.

- lower ureterolithotomy much more difficult than upper & middle third ureterolithotomy
- pre-op KUB to assess precise location and number of stones
- place Foley
- muscle-splitting Gibson incision made in lower quadrant ipsilateral to stone
- sweep peritoneum medially and expose retroperitoneum
- identify ureter as it crosses iliac vessels and place vessel loop
- dissect ureter down towards bladder
- vas deferens crosses ureter in M, uterine artery crosses ureter in F
- stabilize ureter above & below stone with vessel loops
- perform ureterotomy over stone & remove
- use small catheter to irrigate above and below
- place stent
- close ureterolithotomy with interrupted 4-0 dissolvable sutures (eg PDS)
- place JP drain
- close incision in 2 layers
- staples for skin

Chapter #44 – Ureteroscopy and Retrograde Ureteral Access

EQUIPMENT FOR URETEROSCOPY AND RETROGRADE URETERAL ACCESS

What types of ureteroscopes are available?

	Semirigid	Flexible
Details	<ul style="list-style-type: none"> - often tapered and can handle small amount of bend - usually limited to use below iliac vessels 	<ul style="list-style-type: none"> - actively deflectable - usually 120-170 degrees in one direction and 170-270 degrees in the other
Size	<ul style="list-style-type: none"> - 6.75 to 9 Fr 	<ul style="list-style-type: none"> - 6.75 to 9 Fr
Advantages	<ul style="list-style-type: none"> - larger working channel - better irrigation - larger field of view 	<ul style="list-style-type: none"> - can reach entire collecting system, including lower pole
Disadvantages	<ul style="list-style-type: none"> - semi rigid 	<ul style="list-style-type: none"> - inferior image quality - frequent repairs for damaged channel, fiberoptics, or deflection mechanism

What ancillary equipment is required for ureteroscopy and retrograde access?

- OR table (radiolucent)
- fluoroscopy (C-arm)
- video tower and monitor
- ureteral catheters → 5Fr open-ended
→ straight or angled
- guide wires → PTFE coated
→ hydrophilic (obstruction)
→ extra stiff (dilation)
→ double floppy (backload flex ureteroscope)
- dilators → coaxial
→ balloon
- irrigation
- lithotrites → laser, EHL, U/S, ballistic
- working channel instruments → stone graspers
→ stone baskets
- ureteral access sheath → 9-18Fr
- ureteric stents

What are the indications for ureteral dilation?

- rarely required with new smaller ureteroscopes
- inability to pass ureteroscope (<15%)

What are the possible problems with high-pressure irrigation in the upper collecting system?

- higher risk of bacteremia/sepsis → pyelovenous and pyelolymphatic backflow
- distended renal pelvis can limit amount of passive deflection
- can get fluid absorption
- can get significant fluid extravasation

What are the benefits of a ureteral access sheath?

- allows for high-flow, low-pressure irrigation
- easier to insert and remove ureteroscope → makes OR time shorter
- less damage to ureteroscope → decreases costs
- stricture incidence similar to that with ureteroscopy alone → ~1.5%
- higher stone-free rates

What are the different intracorporeal lithotriptors available for ureteroscopy?

- 1) Holmium:YAG laser → gold standard
→ effective and safe
- 2) Nd:YAG laser → not good for COM and brushite
- 3) EHL → poor safety profile
- 4) ballistic → only rigid probes are effective
- 5) U/S → rigid probes only

URETEROSCOPY FOR URETERIC STONES

What are the indications for ureteroscopy (CHART)?

- 1) Diagnostic
 - evaluation for +ve cytology with normal cysto
 - monitoring of previous upper tract TCC
 - evaluation of filling defects on IVP or retrograde
 - undiagnosed gross hematuria
- 2) Therapeutic
 - stones
 - ureteral stricture
 - retrograde endopyelotomy for UPJ obstruction
 - biopsy or ablation of upper tract TCC
 - retrieval of migrated stent or other FB

What is the pre-op preparation for ureteroscopy?

- hx and physical
- imaging
- discussion of possible stent
- urine C&S
- Abx

What are the indications for prophylactic ABx?

- iv ABx for proximal stones or impacted stones
- iv ABx for high-risk patients → DM, significant co-morbidities, etc
- in situ stent
- in situ catheter
- in situ NT
- heart valves or murmurs } new guidelines say no
- prosthetic joint within last 2 years
- prosthetic joint and high risk → immunocompromised (DM, rads, chemo, HIV, malnourished)
- randomized trial by Knopf et al (2003) shows no difference in post-op clinical UTIs (asymptomatic bacteriuria was higher in no ABx group)

How is the patient positioned?

- can use dorsal lithotomy, prone, or flank position
- raise contralateral leg + lower ipsilateral leg → more room to maneuver & aligns ureter
- Trendelenburg for upper ureteric stones → promotes stone fragments to fall into upper calyx

List options for difficult intubation of the U/O during URS (CHART)

- rotate the ureteroscope
- dilate ureteral orifice with 8/10 coaxial dilator over guide wire
- one-step dilation with balloon dilator or serial dilation using coaxial dilators
- placement of ureteral access sheath
- leave JJ stent and defer definitive procedure

What are the indications to leave a stent after URS (CHART)?

- “I Like Inserting Stents For Difficult Procedures”
- **I**nfect + obstructed system
- **L**arge stone burden with many fragments left to pass
- **I**mpacted stone causing ureteral edema
- **S**olitary kidney
- **F**ailure to advance due to narrow orifice or ureter } in prep for repeat URS in 7-10 days
- **D**ilation of ureter performed
- **P**erforation
- to prevent renal colic from stones or edema
- to facilitate stone passage
- to prevent stricture formation

What are the ideal characteristics of a ureteral stent?

- biocompatible
- radiopaque
- relieve intraluminal and extraluminal obstruction
- resist encrustation & infection → should be changed q3-4 months } more frequently in pregnant pt
→ ABx at time of stent insertion may decrease biofilm
- cause little discomfort
- cheap

What types of stents are there?

- 1) material → polyethylene } breaks too easily
→ silicone } too soft
→ blended polyurethane } most stents today
- 2) design → biodegradable
→ spiral stents
→ tail stents } curl in kidney, none in bladder
→ dual durometer } firm kidney curl, soft bladder curl
→ ABx-eluting stents

What is the post-op care following ureteroscopy?

- outpatient surgery
- indwelling stents removed 3-10 days later } after post-op imaging
→ fragments <4mm pass on own after stent is removed (dilated ureter)

What is the role of post-op imaging to r/o obstruction?

- **CONTROVERSY**
- no consensus
- up to 30% have silent obstruction
- **mainly reserved for symptomatic patient, preexisting stricture, ureteral perforation, or impacted stone**

How successful is ureteroscopy for stones?

- distal ureteric stone → >95% stone-free rate (better than SWL 85%)
 - less OR time
 - less fluoro time
 - earlier stone-free status
- proximal stones → >90% stone-free rate (better than SWL 70%)
 - SWL 1st line for 'simple' stones <1cm
 - if >1cm, SWL, ureteroscopy and PNL are all equally viable options
- renal stones → 85-90% stone-free rates
 - ok for stones <2cm, otherwise PNL better
 - LP stones have worse outcomes

What are the indications for URS over SWL for ureteric stones (CHART)?

- "DR, SCOOP Fast Man"
- **D**ense stone (cystine or COM or brushite)
- **R**adiolucent stones
- **S**ize >1cm
- **C**oagulopathy (uncorrected)
- **O**bese (morbid)
- **O**ccupation → pilots must be stone-free
- **P**atient preference
- **F**ailed SWL
- **M**ultiple proximal ureteric stones

URETEROSCOPY IN SPECIAL CASES

Ureteroscopy in Pregnancy

Do pregnant women get stones more often than nonpregnant women?

- NO
- lithogenic factors off-set by increased excretion of inhibitors, etc
- hypercalciuria from increased filtered load and Vit D from placenta
- hyperuricosuria
- increased inhibitors excreted (citrate, Mg, glycoproteins)

What is the management of renal colic in pregnant patients?

- **>80% of women pass stones spontaneously**
- conservative therapy is 1st line therapy } can result in PTL or pyelonephritis
- urgent decompression for urosepsis, azotemia
- avoid GA if possible, especially during T1
 - inhaled agents associated with anomalies – 0.5%
 - increased risk of spontaneous abortion
- **SWL is contraindicated**
- ureteroscopy is safe during pregnancy
 - NO U/S
 - NO EHL

Ureteroscopy in Kids

What is the management of stones in kids?

- similar to adults } PNL, ureteroscopy, SWL
→ SWL first line for most large stone given very distensible ureter
- ureteroscopy (Holmium:YAG, pneumatic, EHL) and stone basketing is safe
- both semi-rigid and flexible ureteroscopy

Ureteroscopy in the Morbidly Obese

What is the role of ureteroscopy in the morbidly obese?

- results similar to ureteroscopy in non-obese } GA concerns, surgical table are issues

Ureteroscopy in patients with coagulopathy

What is the role of ureteroscopy in patients with coagulopathy?

- uncorrected coagulopathy are contraindications to SWL and PNL
- ureteroscopy is a safe alternative
 - avoid EHL } high peak pressure can be transmitted and cause bleeding
 - use only Holmium:YAG
 - avoid high-pressure irrigation
 - minimize ureteral dilation
 - stent all patients

Ureteroscopy for Calyceal Diverticulum

What is the role of ureteroscopy for calyceal diverticulum?

- can be used to manage calyceal diverticular stones → better for UP, anterior tics w/ small stone burden
- identify infundibulum of diverticulum
- pass guide wire into diverticulum
- balloon dilation or Holmium laser incision of narrow neck
- indwelling stent left in situ
- if narrow infundibulum can't be found, percutaneous or laparoscopic approach necessary
- percutaneous neoinfundibulotomy + nephrolithotomy is standard treatment

Ureteroscopy in Anomalous Kidneys

What is the role of ureteroscopy for stones in anomalous kidneys?

- abnormalities in fusion, ascent & form → horseshoe & pelvic ectopic kidneys most common
- ureteroscopy better stone-free rates than SWL
- ureteroscopy is 1st line therapy for small stones
- PNL is 1st line therapy for large stone burden

RETROGRADE URETEROSCOPIC TREATMENT FOR URETERAL STRICTURES

What are the causes of ureteral strictures?

- 1) iatrogenic → ureteroscopy, urinary reconstruction, injury
- 2) RADs
- 3) malignancy
- 4) spontaneous stone passage
- 5) chronic inflammatory disorders (TB, schistosomiasis)

What are the endourologic management options for ureteral strictures?

- Holmium:YAG laser incision
- cold-knife incision
- electrocautery
- hot-wire balloon dilation
- simple balloon dilation → good for short, non-ischemic strictures
- **ischemic strictures usually respond poorly to endourologic procedures**
- endourological procedures are treatment of choice initially } open surgery more successful
but used mainly for failures

What are the predictors of successful endourologic treatment of strictures?

- ischemic vs non-ischemic → ischemic strictures do poorly
- length → <2cm do better
- urine flow through area of incision → necessary for successful endourologic treatment
- poor renal function → if <25% of total renal function, more likely to fail

What are the stricture rates for ureteroenteric anastomoses?

- ileal conduit → 4-8%
- non-refluxing continent urinary diversions (eg Indiana) → 13%
- ureterosigmoidostomy → 22%

What is the role of retrograde endopyelotomy for UPJ obstruction?

- can use laser incision, balloon dilation, hot-wire balloon dilation, laser + balloon
- success rates are ~75% for retrograde endopyelotomy } balloon dilation alone is worst
- patients should be followed for 3 years post for recurrence

URETEROSCOPIC MANAGEMENT OF UPPER TRACT TCC

What is the role of ureteroscopy for upper tract TCC?

- indicated for **diagnostic value** in patient with +ve cytology but normal cysto
- Bx is needed as visual grading accuracy is only 70%
- **can also be therapeutic**
 - renal-sparing technique } Holmium:YAG laser, electrocautery, Nd:YAG laser
 - best for small, low-grade tumours
 - larger tumours should get NephroU or percutaneous resection
 - in select patients, with vigilant f/u, death rate is close to 0%
 - need routine ureteroscopy (q3-6mos) in addition to urine cytology + renal imaging

What is the role of BCG for upper tract TCC?

- can be given antegradely via a NT or retrogradely via stent that refluxes or ureteric catheter
- **controversial as to whether there is any benefit in the upper tract**

COMPLICATIONS OF URETEROSCOPY

What are the complications of URS (CHART)?

- 1) intraop
 - failure to access ureter, kidney, stone
 - failure to fragment stone
 - stone migration into ureteral wall
 - “lost” stone outside ureter
 - mucosal trauma
 - ureteral perforation → <5% } treated with indwelling stent
 } upper ureter more susceptible (thinner muscularis)
 - ureteral avulsion → usually occurs during basketing } telescoping + avulsion
 → requires open surgery (UU, reimplant, ileal interposition,
 autotransplantation, or nephrectomy)
- 2) early post-op
 - gross hematuria
 - renal colic (stone fragments, clot, ureteral edema)
 - large residual stone fragments needing ancillary procedure
 - pyelonephritis/urosepsis
 - urinoma
 - ureteral stent symptoms
- 3) late post-op
 - ureteral stricture → 4-5%
 - retained encrusted stent

What are the RFs for ureteral perforation during/after ureteroscopy?

- 1) long OR time
- 2) use of EHL
- 3) impacted stone
- 4) surgeon inexperience
- 5) renal stones

- renal papilla → divides renal parenchyma from collecting system
- minor calyx → 5-14 (mean 8)
 - drain directly into infundibulum or join to form major calyces
- major calyces → superior, mid, lower groups
 - polar groups are usually compound (>2 minor calyces/renal papillae)
 - midzone usually consist only of anterior and posterior
 - 2 configurations (see below)
- infundibula → principal divisions of the pelvicalyceal system, draining directly into renal pelvis
 - superior calyceal group is almost always drained by 1 midline infundibulum
 - midzone calyceal group is almost always drained by paired calyces arranged in 2 rows (Ant & Post)
 - **safest access is directly into the fornix of a calyx, through the renal papillae**

What are the 2 common configurations of the midzone calyces?

- 1) Brodel configuration } more common on R
→ posterior midpole calyx is long and points laterally
→ anterior midpole calyx is short and points anteriorly
- 2) Hodson configuration } more common on L
→ posterior midpole calyx is short and points posteriorly
→ anterior midpole calyx is long and points laterally

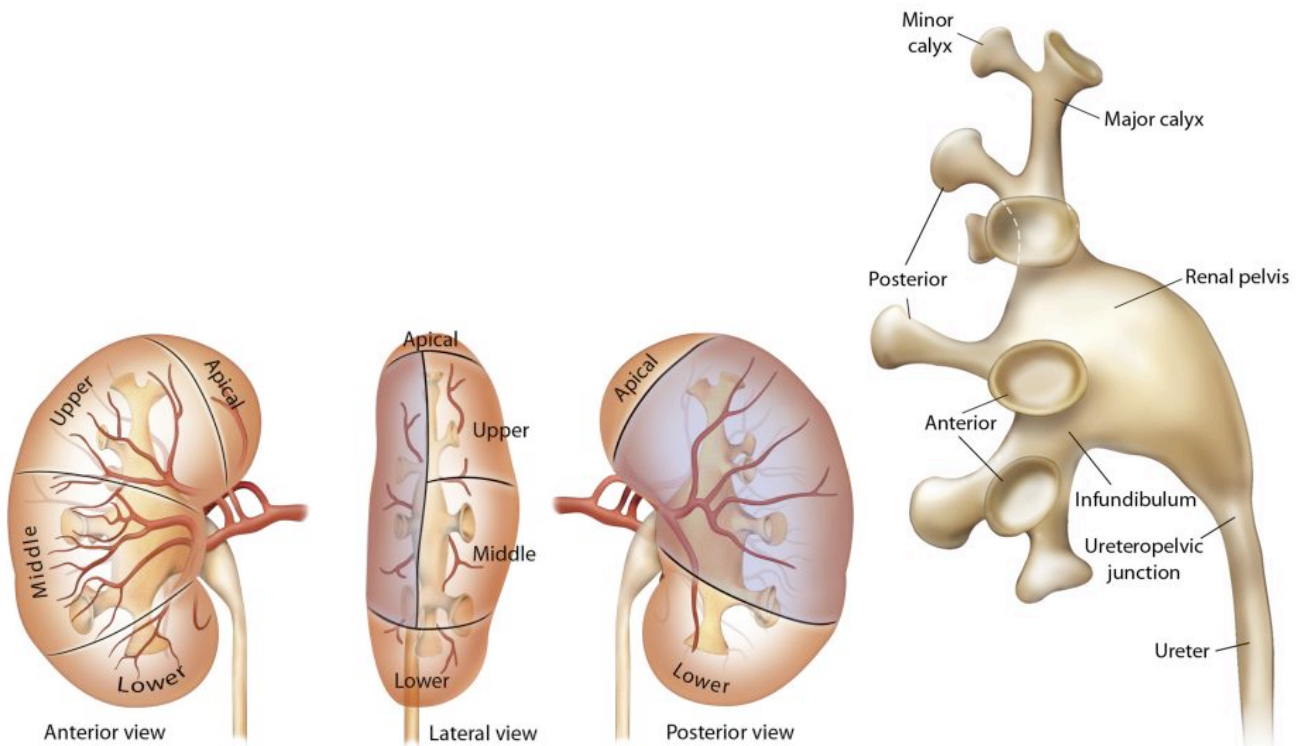
What is the most commonly injured renal vessel in endourologic surgery?

→ **posterior segmental artery**

- usually located in the middle or upper half of the posterior renal surface
- can be damaged with a very medial needle puncture of an upper calyx

What are the 3 factors to consider once a calyx is chosen?

- 1) relation to 12th rib
- 2) extent of hydro
- 3) presence of malrotation



IMAGING FOR PERCUTANEOUS ACCESS

What are the different imaging modalities employed to gain access into the renal collecting system?

- U/S → mainly for percutaneous drainage of obstructed, infected system
- fluoroscopy
- CT
- MRI
- “blind access”

What are the advantages & disadvantages of the different imaging modalities used to gain access?

	ADVANTAGES	DISADVANTAGES
U/S	<ul style="list-style-type: none">- avoids radiation- can see structures between skin and kidney- easy to identify hydronephrosis- highly successful (~95%)- low complication rate (5%)	<ul style="list-style-type: none">- technically demanding- hard to identify needle tip- difficult if no hydronephrosis- can't clearly visualize guide wire for manipulation
Fluoro	<ul style="list-style-type: none">- doesn't require hydronephrosis- can visualize needle tip and guide wire easily	<ul style="list-style-type: none">- radiation exposure- requires retrograde access for contrast
CT and MRI	<ul style="list-style-type: none">- provides sophisticated pre-op information- required if upper pole, supra-11th access needed- good for difficult cases eg obese, malrotated, large staghorn	<ul style="list-style-type: none">- time-consuming- expensive

What are the recommendations regarding radiation exposure?

- **ALARA → as low as reasonably achievable**
- maximum yearly whole-body exposure recommended by the National Council on Radiation Protection is 5000 mrem or 5 rem
- limit exposure TIME
- increase DISTANCE from patient and radiation source } inverse square law
- SHIELDING (minimum 0.5mm thickness)

What are methods to decrease radiation exposure during endourology?

- grid-controlled fluoro
- aim more midline (less scatter)
- use of last-image-hold function (minimize fluoro time)
- collimation (narrows beam and thus scatter)
- place fluoro beam under table (less leakage and scatter)
- use lead aprons & thyroid shields +/- lead gloves

What are the indications for blind access?

→ **rarely, if ever indicated**

- retrograde or iv opacification precluded AND pelvicalyceal system can't be opacified
AND U/S or fluoro inaccessible

Describe the lumbar notch.

- for blind access } aim 18gauge needle cephalad, under 12th rib, to a depth of 3-4cm
- superior border → latissimus dorsi and 12th rib
- medial border → sacrospinalis and quadratus lumborum muscles
- lateral border → transversus abdominis and external oblique muscles
- inferior border → internal oblique muscle

RETROGRADE AND RETROGRADE-ASSISTED PERCUTANEOUS RENAL ACCESS

What are the benefits of retrograde nephrostomy?

- safe
- short learning curve
- minimal radiation

What clinical situations are amenable to retrograde-based percutaneous renal access?

- 1) morbid obesity
- 2) tightly branched staghorn stone
- 3) hypermobile kidney
- 4) malrotated kidney
- 5) ptotic kidney

What are the 2 methods of retrograde access?

- 1) ureteroscopically assisted percutaneous access
 - fluoroscopically guided puncture aimed at end of ureteroscope
 - confirmed under direct vision endoscopically
 - guide wire snared/basketed and brought out with ureteroscope through urethra
- 2) retrograde percutaneous access
 - sharp wire passed under fluoroscopic guidance through a ureteral catheter and directed out the selected calyx
 - very NB not to dilate tract until certain tract is sufficiently posterior and inferior to injury to adjacent organs

TECHNICAL ASPECTS OF PERCUTANEOUS ACCESS

What are the different options for ureteral catheterization?

- 1) open-ended catheter → nonobstructive (low intrarenal pressures)
 - minimal risk of ureteral injury
 - }}} doesn't prevent migration of stone fragments down ureter
- 2) double-lumen catheter → retrograde injection of 2 mediums (eg contrast and indigo carmine)
 - nonobstructive } injection and drainage (low intrarenal pressures)
 - simultaneous guidewire and medium injection
 - prevents stone migration down ureter
 - }}} may cause ureteral edema
- 3) occlusion balloon → prevents fragment migration down ureter
 - }}} can cause ureteral injury
 - }}} high intrarenal pressures
- 4) ureteral access sheath → facilitates fragment passage
 - nonobstructive (low intrarenal pressures)
 - allows for injection of medium
 - }}} can cause ureteral injury
 - }}} hard to adequately drain bladder

What are the principles of percutaneous tract selection?

- posterior calyx preferred
 - easier to access renal pelvis cf anterior calyx
 - in general, posterior calyces are more medial (think Hodson configuration of midpole calyces)
 - avoids vasculature
 - transparenchymal route stabilizes nephrostomy catheter
- don't directly puncture renal pelvis
 - avoids large vessels
 - no stability
 - decreases extravasation
- subcostal approach preferred
 - go below the 12th rib when possible
 - hard to directly access UP calyx by subcostal approach, so intercostal approach may be req'd
- use the C-arm in different planes to assess location of puncture/access

DILATION OF NEPHROSTOMY TRACT

What are the different types of nephrostomy tract dilators?

- 1) fascial dilators
 - 8-36Fr Teflon tubes that slide over guide wire
 - relies on integrity of guide wire
 - relatively safe and good for fibrous tracts
- 2) malleable dilators
 - Amplatz dilators (12-30Fr) with access sheath
 - dilating catheters slid over 8Fr tapered catheter + guide wire combo
 - stable and relatively safe
- 3) metal coaxial dilators
 - telescopic stainless steel dilator (9-24Fr)
 - good for very fibrous tracts
 - hard to control the pressure exerted
- 4) balloon dilators
 - balloon catheter with back-loaded working sheath
 - may see waist at areas of high resistance (fascia, previous scar, renal capsule)
 - no need for serial dilation
 - less renal hemorrhage and lower transfusion rates cf Amplatz dilators

COMPLICATIONS OF PERCUTANEOUS RENAL SURGERY

What are the complications of percutaneous renal surgery?

→ 8% complication rate for direct UP puncture

→ access-related

- bowel injury (colon, duodenum, pancreas) } <1%
- injury to liver or spleen
- pneumothorax/hemothorax
- lung injury
- hemorrhage
- positioning injury (nerve palsy, etc))

→ procedure-related

- hemorrhage
- renal pelvic injury
- ureteric injury
- fluid absorption } mainly if perforation or venous injury ... can get TUR syndrome
- pleural effusion
- extravasation
- unable to find stone OR loss of stone through perforation
- incomplete lithotripsy
- sepsis (1-2%)
- renal AVF

What are the RFs associated with an increased risk of bleeding during percutaneous renal surgery?

- excessively medial puncture
- multiple punctures
- abnormal renal anatomy
- bleeding diathesis

What is the management of hemorrhage during PNL?

- conservative mgt sufficient for most cases
- for tract bleeding can use large-bore NT or Kaye catheter (tamponading)
- council balloon catheter can be used for venous bleeding
- **delayed bleeding almost always due to AVF or pseudoaneurysm**
- <1% need angio + embolization } 40% AVFs, 35% pseudoaneurysms
- 3-23% transfusion rate

What is the management of renal pelvic perforation?

- usually due to aggressive passage of dilators or lithotripter
- should stop PNL and place ureteral stent + NT

What is the management of lung complications of PNL?

- highest risk with intercostal approach between 10th and 11th ribs
- pleural effusion in ~8%, pneumothorax in 4%
- post-op CXR for all intercostal PNLs
- small effusions seen intra-op may be tapped
- large effusions, hemothorax, or pneumothorax may require a chest tube

What are the RFs for colonic injury during PNL?

- thin F
- abN renal anatomy (horseshoe, ectopic, etc)
- previous jejunoileal surgery
- NH patients
- anterior calyceal puncture
- previous renal surgery

What are the signs of colon perforation during PNL?

- intraop hematochezia or diarrhea
- peritonitis
- sepsis
- gas or feces drainage from NT
- contrast in colon during post-op nephrostogram

What is the management of a colonic injury during PNL?

- place ureteric stent
- pull back NT and use as colostomy tube for extraperitoneal perforation
- antibiotics
- NPO } consider TPN
- imaging in 1wk + removal of perc tube if no communication with GU tract
- laparotomy for intraperitoneal injuries or the presence of peritonitis/sepsis

What is the management of splenic or liver injuries during PNL?

- rare unless hepatosplenomegaly } should get CT-guided access
- splenic injuries usually require laparotomy +/- splenectomy
- liver injuries can usually be managed conservatively

PERCUTANEOUS PROCEDURES OF THE UPPER URINARY TRACT

Obstruction

What is better in the setting of obstruction and pyelonephritis, ureteral stenting or NT?

- CONTROVERSIAL } NT better in one RCT (Mokhmalji et al 2001)
- } no difference in another RCT (Pearle et al 1998)
- more discomfort and irritative symptoms with stent (Joshi et al 2001)

What is the management for MUO?

- NT recommended for advanced abdo/pelvic malignancies
- placing 2 ureteral stents may be beneficial

Pyonephrosis and Emphysematous Pyelonephritis

What is the management of pyonephrosis or pyocalyx?

- usually occurs secondary to an obstructing stone in a patient with infected urine
- acute or chronic
 - acute → immediate NT insertion
 - chronic → may be afebrile, may have sterile urine, may see “phantom” calyx
 - NT drainage
- subcostal approach only → prevents pulmonary complications (eg empyema)

What is the management of emphysematous pyelonephritis?

- 1) NT insertion + iv Abx
 - viable option, esp for those too unstable to tolerate OR or can't afford to lose kidney
 - avoid injection of contrast in setting of emphysematous pyelo
 - subcostal approach only } prevents pulmonary complications (eg empyema)
- 2) immediate nephrectomy
 - still gold standard Rx

Renal Cysts

What are the management options for symptomatic benign renal cysts?

- 1) aspiration alone → 10-20% resolution
- 2) aspiration + sclerotherapy → 80% resolution } little long term data
- 3) percutaneous resection → 90% resolution } little long term data
- 4) laparoscopic cyst decortication
- 5) open cyst decortication

What are the indications for percutaneous resection of renal cysts?

- patients failing aspiration + sclerotherapy
- cysts that communicate with the collecting system
- cysts too large to be adequately treated by aspiration + sclerotherapy

What are the materials used for renal cyst sclerotherapy?

- 95% ethanol
- tetracycline
- povidine-iodine
- polidocanol 3%
- bismuth phosphate

What findings on aspiration of renal cysts are suggestive of malignancy?

- sanguinous fluid (may also be traumatic puncture)
- nodularity of the cyst wall seen on opacification

Calyceal Diverticula

What are the indications to treat calyceal diverticulum?

- pain
- hematuria
- progressive renal damage
- recurrent UTIs
- symptomatic stones

What are the management options for calyceal diverticulum?

- 1) excision of diverticulum
- 2) open or laparoscopic marsupialization + occlusion of neck (suture or cautery)
- 3) percutaneous fulguration +/- dilation of neck → 80% success rate
 - stone-free rates ~85%
 - DIRECT approach only; indirect approach not successful
- 4) ureteroscopic dilation of neck +/- fulguration
- 5) ESWL +/- ureteroscopic dilation of neck → poor results with ESWL alone
 - stone-free rates only 70%
- 6) partial nephrectomy } for large diverticulum

Infundibular Stenosis

How does infundibular stenosis usually present?

- may have flank pain, hematuria, UTIs, or rarely progressive renal damage
- on imaging may have hydrocalyx } may be hard to differentiate from calyceal diverticulum
 - } no renal papilla in diverticulum
- may have complete stenosis, resulting in an excluded calyx

What are the causes of infundibular stenosis (hydrocalyx)?

- 1) extrinsic
 - retroperitoneal malignancy
 - retroperitoneal fibrosis
 - Fraley's syndrome (UP infundibular obstruction by crossing superior segmental artery)
- 2) intrinsic
 - cancer
 - TB
 - chronic scarring from recurrent stones or a long-standing stone
 - prior renal surgery

What are the indications to treat infundibular stenosis?

- pain
- recurrent UTIs
- progressive renal damage (rare)
- symptomatic stones

What are the management options for infundibular stenosis?

- 1) percutaneous antegrade procedure } only 60-80% success rate
 } not as good as Rx for calyceal diverticulum
 - balloon dilation
 - incision (cold or laser)
 - electrocauterization
- 2) retrograde placement of guide wire with antegrade cut-down } for excluded calyx

Fungal Bezoars

What are fungal bezoars?

- very rare infectious concretions of the kidney
- associated with fulminant fungal pyelo AND asymptomatic funguria
- variable presentation } obstruction, gross hematuria, sepsis
- usually *Candida* species but can also be from *Aspergillus*
- grey-white or yellow-grey appearance

What are the RFs for fungal bezoars?

- DM
- neurogenic bladder
- chronic Abx use
- indwelling urinary catheters
- elderly patients
- immunocompromised patients eg HIV, transplant
- premature infants

What is the management of fungal bezoars?

- iv antifungal Rx } amphotericin B or flucytosine
- topical irrigation with amphotericin B (50mg/L at 50cc/hr)
 - via NT
 - via 2 ureteral catheters (one for irrigation and the other for drainage)
- percutaneous removal
 - after sterile urine
 - subcostal approach to avoid pulmonary complications
- 80% success rate

Fibroepithelial Polyps

What are fibroepithelial polyps?

- rare benign mesodermal tumours
- long slender projections w/ a smooth surface presenting as single or multiple fronds coming from a common base
- fibrovascular stroma from submucosa covered by nonpapillary transitional cell epithelium
- most commonly found in young patients → hematuria and flank pain
→ can be an uncommon cause of UPJO in kids

What are the indications for treatment of fibroepithelial polyps?

- high degree of
→ obstruction
→ urinary tract involvement
→ suspicion for TCC

What are the management options for fibroepithelial polyps?

- percutaneous resection

Ureteroenteric Anastomotic Strictures

What are the causes of ureteroenteric anastomotic strictures?

- early → ureteral ischemia
- late → fibrosis
→ progression of malignant disease

What are the indications for treatment of ureteroenteric anastomotic strictures?

- 1) recurrent infections
- 2) recurrent stones
- 3) pain
- 4) renal dysfunction

What are the management options for ureteroenteric anastomotic strictures?

- 1) percutaneous antegrade procedures
→ incision (cold knife, laser) } ~50% success over 2yrs
→ balloon dilation
- 2) open reimplantation
→ very difficult due to dense scarring and adhesions
- 3) retrograde approach very difficult

NEPHROSTOMY DRAINAGE

What are the indications for the placement of post-percutaneous drainage devices?

→ tubeless percutaneous surgery has been reported and seems safe and feasible in SELECT PATIENTS

→ **post-op drainage is the standard of care**

→ type of drainage device depends on:

- complicated vs uncomplicated procedure
- degree of bleeding
- likelihood of obstructing edema
- likelihood of repeat intervention
- patient tolerability
- endourologist's preference

What are the different types of post-percutaneous drainage devices?

- 1) Malecot tubes → good drainage
→ poorly secured
→ not good for bleeding
- 2) pigtail catheters → slightly more secure, good drainage, and easy to insert
→ Cope loop catheter more secure, soft, and high coefficient of friction
 - hard to remove if end becomes encrusted or loop doesn't unfurl
 - string left in collecting system can serve as nidus for stones
 - may be hard to coil loop in small renal pelvis
→ not good for bleeding
- 3) balloon retention catheters → very secure and can be used to tamponade bleeding
- 4) re-entry tubes → malecot with 18cm distal extension (5-8Fr)
→ good drainage, soft, easily removed and maintains good ureteral access
→ poorly secured
- 5) circle loop NT → easily changed, rarely causes infection and stones, causes little intrarenal trauma, can be used for irrigation, and good for long-term

What is the role of tubeless nephrostomy and fibrin glue in the tract?

- shown to be safe and feasible in select patients } double J ureteral stent placed for all
 - no significant post-op bleeding
 - no perforation or extravasation
 - no obstruction
 - low risk of ureteral edema
 - repeat nephroscopy NOT required } limited to no residual stone burden
 - short OR time
- unclear as to clinical benefit after percutaneous renal surgery } 2nd procedure to remove stent

What is the role of cauterization of the access tract?

- difficult to fulgurate bleeding of renal parenchymal origin
- bleeding may be aggravated rather than diminished

FUTURE DIRECTIONS

What are some innovations in obtaining access?

- PAKY } fluoroscopic-based robotic arm with active remote centre of motion translational device for percutaneous access to the kidney (PAKY-RCM)
 - } monitors path and depth of needle insertion
- Smart Needle } uses impedance differences detected between renal parenchyma and urine
- ureteroscopically assisted access } advanced flexible dial active deflection scopes
eg Storz Flex-X

Chapter #47 – Renal Tumours

CLASSIFICATION

Tumors of the Renal Capsule

- Fibroma
- Leiomyoma
- Lipoma
- Mixed

Tumors of the Mature Renal Parenchyma

- Adenoma
- Adenocarcinoma
- Hypernephroma
- Renal cell cancer
- Alveolar carcinoma

Tumors of the Immature Renal Parenchyma

- Nephroblastoma (Wilms')
- Embryonic carcinoma
- Sarcoma

Epithelial Tumors of the Renal Pelvis

- Transitional cell papilloma
- Transitional cell carcinoma
- Squamous cell carcinoma
- Adenocarcinoma

Cysts

- Solitary
- Unilateral multiple
- Calyceal
- Pyogenic
- Calcified
- Tubular ectasia
- Tuberous sclerosis
- Cystadenoma
- Papillary cystadenoma
- Dermoid
- Pararenal/Perirenal cysts
- Hydrocele renalis
- Lymphatic
- Wolffian
- Malignant

Vascular Tumors

- Hemangioma
- Hamartoma
- Lymphangioma

Neurogenic Tumors

- Neuroblastoma
- Sympathicoblastoma
- Schwannoma

Heteroplastic Tissue Tumors

- Adipose
- Smooth muscle
- Adrenal rests
- Endometriosis
- Cartilage
- Bone

Mesenchymal Derivatives

- Connective tissue
- Fibroma
- Fibrosarcoma
- Osteogenic sarcoma
- Adipose tissue
- Lipoma
- Liposarcoma
- Muscle tissue
- Leiomyoma
- Leiomyosarcoma
- Rhabdomyosarcoma

Pararenal/Perirenal Solid Tumors

- Lipoma
- Sarcoma
- Liposarcoma
- Fibrosarcoma
- Lymphangiosarcoma
- Cancer
- Teratoma
- Lymphoblastoma
- Neuroblastoma
- Hodgkin's disease

Secondary Tumors

- Cancer
- Sarcoma
- Blastoma
- Granuloma
- Thymoma
- Testicular
- Renal

→ Deming and Harvard (1970)

What is the classification of renal masses based on pathology?

1) Malignant

→ RCC

- conventional (clear cell)
- papillary
- chromophobe
- collecting duct
- undifferentiated

→ urothelial

- TCC
- SCC
- adenocarcinoma

→ sarcoma

- leiomyosarcoma (most common)
- liposarcoma
- angiosarcoma
- hemangiopericytoma
- rhabdomyosarcoma
- malignant fibrous histiocyoma (MFH)
- synovial sarcoma
- osteogenic sarcoma
- clear cell sarcoma
- carcinosarcoma

→ Wilm's tumour

→ primitive neuroectodermal tumour

→ carcinoid

→ lymphoma

→ leukemia

→ metastases

→ invasion by adjacent neoplasm

2) Benign

→ simple cyst

→ AML

→ oncocytoma

→ renal adenoma

→ metanephric adenoma

→ cystic nephroma

→ mixed epithelial-stromal tumour

→ leiomyoma

→ fibroma

→ hemangioma

→ vascular } renal artery aneurysm } AVM

→ pseudotumour

→ reninoma (JG cell tumour)

3) Inflammatory

→ abscess

→ focal pyelonephritis

→ xanthogranulomatous pyelonephritis (XGP)

→ infected renal cyst

→ TB

→ rheumatoid granuloma

RADIOLOGIC EVALUATION OF RENAL MASSES

What features on IVP are suggestive of a renal mass?

- low sensitivity & specificity
 - 1) calcification within mass
 - 2) increased tissue density
 - 3) irregularity of the margin
 - 4) distortion of collecting system
- if benign mass suspected on IVP, order an U/S
- if malignant mass suspected, order CT

What are the U/S findings of a simple cyst?

- 1) smooth cyst wall
 - 2) anechoic
 - 3) round or oval shape
 - 4) no internal echoes/vascular flow
 - 5) through-transmission with strong acoustic shadows posteriorly
- if not a simple cyst, order a CT

What are the U/S findings of an AML?

- fat has characteristic increased echogenicity (**hyperechoic - whitish on U/S**)
- lesion has associated shadowing } RCC usually does not shadow

What are the 3 phases of a triphasic CT to assess renal masses?

- 1) **unenanced phase** } identify fat, calcifications, general renal contour
 - 2) **corticomedullary phase (~30 sec)** } arterial enhancement
 - cortex distinct from medulla
 - **tumours enhance more than background**
 - 3) **nephrographic phase (~100 sec)** } assessment of enhancement
 - uniform enhancement of parenchyma
 - **renal masses most easily detected in this phase**
 - **tumours enhance less than background**
- **10-20 HU enhancement is “equivocal” } may need MRI**
→ **>20 HU enhancement is “significant enhancement”**
→ **fat is less than - 10HU on CT**

What are the CT findings of an AML?

- fat + no calcification is diagnostic } **below -20 HU (BUT, if + calcifications, think RCC)**

What is the DDx of a fat-containing renal mass? (includes AUA Update #32 – 2007)

- | | |
|----------------------|------------------|
| 1) AML | 4) Wilms' tumour |
| 2) renal lipoma | 5) oncocytoma |
| 3) renal liposarcoma | 6) teratoma |

What are the CT findings of a pseudotumour?

- enhancing mass that is isodense with remainder of kidney
- Dx confirmed by DMSA renal scan } increased uptake if pseudotumour, decreased if RCC

What is the DDx of a renal pseudotumour?

- 1) hypertrophied column of Bertin
- 2) dromedary hump
- 3) renal dysmorphism (malrotation, duplication)
- 4) fetal lobulation

What are the CT findings of a RCC?

- mass that enhances with contrast } **≥ 15-20 HU enhancement is RCC until proven otherwise**
- heterogeneous
- ~10% of renal masses are equivocal on CT

What are the MRI findings of a RCC?

- T1 weighted } enhancing mass with gadolinium

Why is angiography not a reliable diagnostic test for RCC?

- 20-25% of RCCs are angiographically indistinct

List features on angiography suggestive of RCC?

- hypervascular
- hypovascular
- random distribution of vessels
- tortuous vessels w/o N tapering
- dilated vessels w/ pooling of contrast ("lakes" of contrast)
- AVF (early venous phase)
- encasement of arteries
- staining of tumour mass during (capillary phase)
- renal vein invasion w/ or w/o obstruction
- lack of response of vessels to epinephrine

What are the characteristics of a cyst used to classify risk of malignancy?

- wall → thickness and contour
- septa → number, thickness, and contour
- calcifications → amount, character, location
- fluid density
- presence of solid components
- cyst margin

Define the Bosniak classification of renal cysts (originally based on CT)?

- 1) Bosniak I cyst
 - thin walls, homogeneous, sharp interface with surrounding tissue, no septations, no calcifications, no enhancement, HU 0-20
 - **NO risk of RCC** } simple cyst
 - Rx → NO treatment or surveillance
- 2) Bosniak II cyst
 - few thin septations
 - minimal calcification of wall or septum
 - can have small hyperdense cysts (>20 HU + don't enhance + ≤3cm)
 - **1-5% risk of RCC**
 - Rx → periodic surveillance imaging

Bosniak IIF (follow-up)

 - many thin septations
 - nodular thick calcifications
 - large hyperdense cyst (>20HU + don't enhance + >3cm)
 - **10-15% risk of RCC**
- 3) Bosniak III cyst
 - irregular or thick margin
 - thick or irregular septa (updated classification includes mildly enhancing septa)
 - thick or irregular calcifications
 - **40-50% risk of RCC**
 - Rx → Sx if no hx of renal trauma or infection
- 4) Bosniak IV cyst
 - large cystic component
 - irregular, shaggy margin
 - solid enhancing component
 - **70-90% risk of RCC**
 - Rx → Sx } cystic RCC until proven otherwise

How common are benign, solid, enhancing masses?

- 10-20% of renal masses suggestive of RCC on imaging are benign on pathology

What are the indications for FNA or Bx of a renal mass?

- r/o infected cyst or abscess
- r/o met
- r/o renal lymphoma
- to confirm diagnosis in poor surgical candidate prior to going ahead with Sx
- prior to ablative therapy
- renal failure NYD
- genetic syndrome with multifocal tumours

BENIGN RENAL TUMOURS

List some benign renal tumours.

→ women more likely to have benign masses

→ SRMs more likely to be benign also (35% vs 20%)

- | | |
|--------------------------|---|
| - pseudotumour | - cystic nephroma |
| - benign renal cyst | - mixed epithelial stromal tumour of the kidney (MESTK) |
| - renal cortical adenoma | - leiomyoma |
| - metanephric adenoma | - hemangioma |
| - oncocytoma | - reninoma (JG cell tumour) |
| - AML | - vascular } renal artery aneurysm, AVM |
| - lipoma | - fibroma |

What is a benign renal cyst?

- most common benign renal mass (70% of asymptomatic masses)
- **more common in M (2:1)**
- prevalence increases with age (50% of 50yr olds)
- mean growth of 3mm/yr

Rx → observation unless symptomatic

- perc drain +/- sclerosis (alcohol – don't use if near renal hilum)
- lap marsupialization

What is a renal cortical adenoma?

- **usually solitary but 25% are multicentric**
- **more common in M (3:1) and ?smoking association**
- incidence increases with age
- **more common in VHL and ARCD**
- small, well-circumscribed lesion with uniform basophilic or eosinophilic cells
- tubulopapillary or purely papillary growth

Rx → histologically **difficult to differentiate from papillary RCC**

- controversial diagnosis } should consider Rx as RCC

What is a metanephric adenoma?

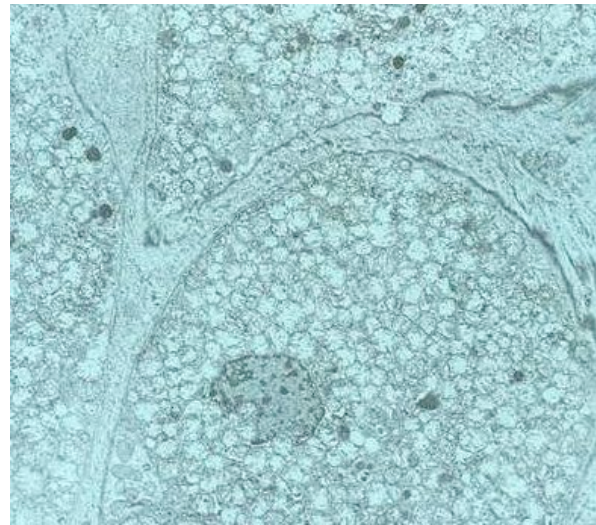
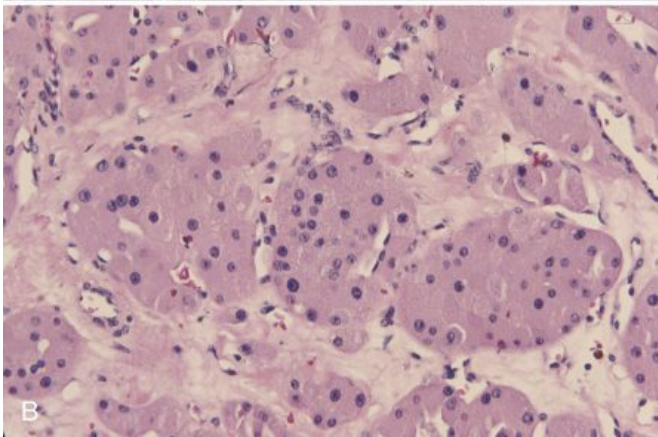
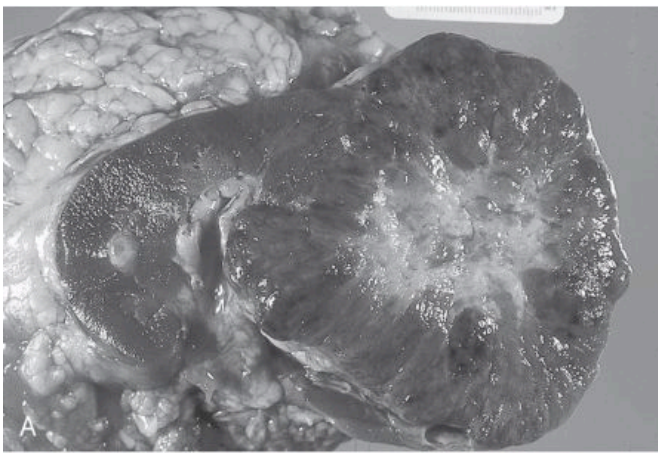
- **slightly more common in M**
- peak incidence in 40s
- **often present as large (mean 5.5cm) asymptomatic masses**
- small basophilic cells with tubular or papillary structures within a mainly acellular stroma
- **similar to Wilm's tumour or papillary RCC**

Rx → Sx recommended

- pathologic Dx only

What is an oncocytoma?

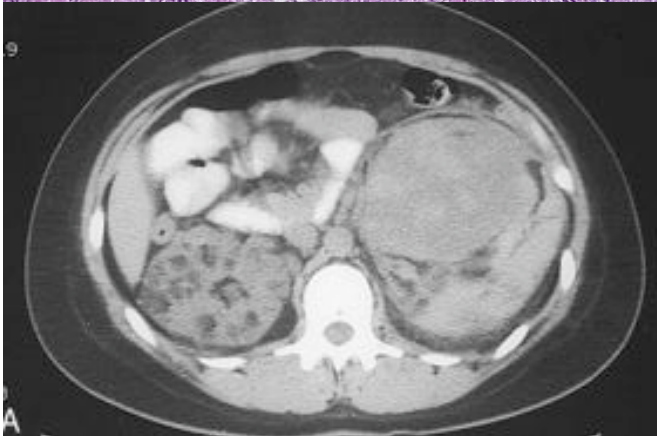
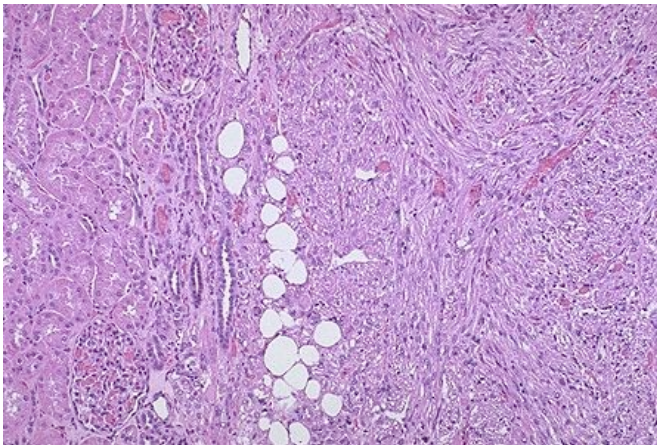
- light brown or tan, homogeneous, well-circumscribed lesions
 - **central stellate scar** with spoke-wheel pattern of feeding vessels on angio
 - lacks hypervascularity & necrosis
 - **eosinophilic cells** in nested or organoid appearance
 - **packed with large mitochondria on EM** } **classic finding**
 - **-ve for Hale's colloidal stain on histology (chromophobe RCC is +ve Hale's)**
 - may have prominent nucleoli or extend into perinephric fat
 - abnormalities on chromosomes Y, 1, 11, 14
 - NEVER on chromosomes 3, 7, 17
 - from **intercalated CD cells** like chromophobe RCC } both **more common in Birt-Hogg-Dube**
 - tend to be **multicentric, bilateral, with metachronous recurrence**
 - **up to 30% chance of RCC in same or contralateral kidney**
- Rx → Sx recommended } can't reliably Dx oncocytoma even on FNA or Bx



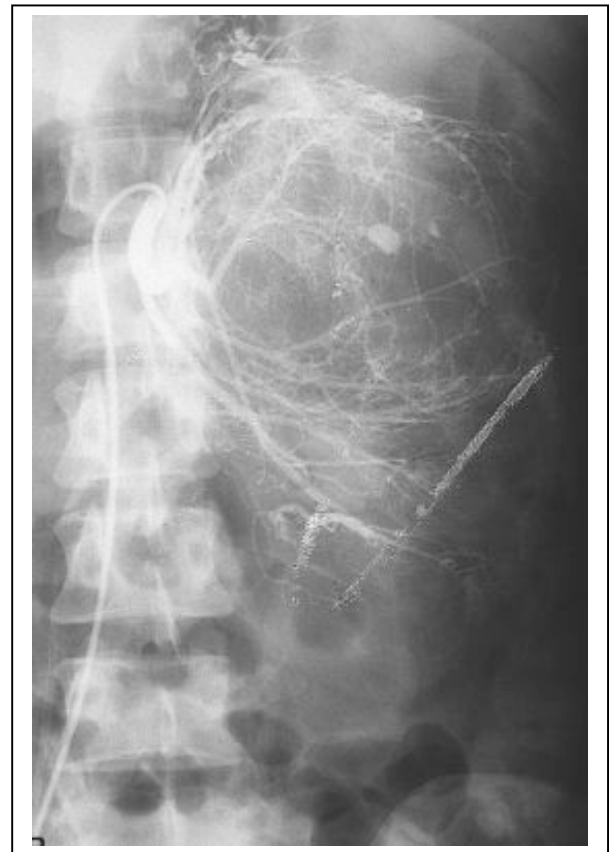
→ ONCOCYTOMA } central stellate scar, nests of eosinophilic cells, large mitochondria on EM

What is an AML?

- benign clonal tumour of varying amounts of **vessels, smooth muscle, and fat**
 - few rare cases of malignant variants (eg **malignant epithelioid variant**)
 - aneurysmal dilatation of vessels can be present
- from **perivascular epithelioid cells (PEC-omas)**
- **more common in F and rare before puberty } hormone-dependent growth**
- slow growth } mean growth rate ~5% per yr
- 25-30% are bilateral } 65-80% bilateral in TS
- **20-30% of AMLs are assoc'd w/ Tuberous Sclerosis } 80% sporadic**
 - retardation, epilepsy, skin adenoma sebaceum, renal cysts } **50% with TS get AMLs**
 - AD disorder with variable penetrance } AMLs present earlier
 - TSC1 on chromosome 9 (hamartin)
 - TSC2 on chromosome 16 (tuberin) } more common & associated w/ worse features
 - more likely to be bilateral, multicentric, and grows faster than solitary AMLs not associated with TS (more likely to need surgery)
 - RCC develops in 1-3% with TS (less aggressive w/ better survival)
- **Wunderlich's syndrome found in 10% } massive retroperitoneal hemorrhage**
 - } ↑'d risk with pregnancy & more common on L
- 15% can develop ESRD } more common with TS
- **fat (< -20 HU) + no calcifications is diagnostic } lipid-poor AML makes Dx tough (15%)**
 - **NEVER has calcifications } 5 cases of AML and RCC all had calcifications**
- **hyperechoic on U/S**
- **light on T1 MRI and dark on T2 MRI**
- **+ve for HMB-45 & Melan-A stains } differentiates from often similar sarcomas**
- **always -ve for cytokeratin stain } RCC is always +ve**



→ AML (Tuberous Sclerosis)



List common features of Tuberous Sclerosis.

- **mental retardation**
- renal cysts (35%)
- renal AMLs (~50%)
- RCC (1-3%)
- pheochromocytoma
- **epilepsy**
- cortical tubers
- retinal hamartomas
- subependymal nodules
- **skin adenoma sebaceum (facial angiofibromas – reddish spots or bumps)**
- ungal or subungal (nails) fibromas
- ash leaf spots (white spots)
- Shagreen patches
- bone cysts
- lung lymphangioleiomyomatosis (LAM) } almost exclusively in young females
- cardiac rhabdomyomas



→ ASH LEAF SPOT



→ SHAGREEN PATCH

List common sites of AMLs (AUA Update #32 – 2007)

- **renal (most common by far)**
- liver
- hilar LNs, retroperitoneum, skin, lung, colon (rare)

List common causes of spontaneous perinephric hemorrhage.

- 1) **AML (~50%)**
- 2) RCC (~20%)
- 3) periarteritis nodosa
- 4) renal artery aneurysm
- 5) renal vein thrombosis
- 6) other benign & malignant tumours

List management options for renal AMLs (includes AUA Update #32 – 2007)

- 1) active surveillance + serial imaging (q6-12 months) } if <4cm + asymptomatic
- 2) selective arterial embolization \ preferred option for multicentric AMLs,
- 3) partial Nx / AMLs associated w/ TS, or renal insufficiency
- 4) radical Nx
- 5) cryoablation (limited data)
- 6) rapamycin (trials)

List indications for treatment of renal AMLs. (includes AUA Update #32 – 2007)

- ≥4cm
- symptomatic (pain, hematuria, bleed, etc)
- F of childbearing age (planning pregnancy, on OCP, etc)
- suspicion of RCC

List common complications of selective embolization of AMLs.

- abscess (most common – 5%)
- pleural effusions (3%)
- post-embolization syndrome (up to 85% but transient) } flank pain, fever, leukocytosis, nausea
Rx → steroids can ↓ syndrome to <30%

What is a cystic nephroma?

- aka **“multi-loculated cystic nephroma”**
 - benign well-circumscribed, encapsulated multiple cysts partitioned by septa
 - bimodal age distribution } **age 2 or 3 then again in 30's or 40's**
 - usually **unilateral, unifocal, and central**
 - **M predominance in kids but F predominance in adults**
 - kids usually asymptomatic while adults usually have abdo pain, hematuria, UTI, HTN
 - **10% have calcification + herniation into collecting system**
 - **can't reliably differentiate from cystic RCC (Bosniak 4) or cystic Wilms'**
 - most lesions are HYPOvascular
- Rx → Radical Nx because of concern for RCC/Wilms'
→ PNx if amenable

What is a Mixed Epithelial-Stromal Tumour of the Kidney (MESTK)?

- **mixture of epithelial & stromal elements** that form solid and cystic growth patterns
 - grossly cystic and **resembles Bosniak III-IV cysts on imaging**
 - may be related to cystic Wilms' } spectrum of disease
 - mainly in **perimenopausal women who are on estrogen** } most stain +ve for estrogen receptor
- Rx → PNx if suspected (benign course)

What is a leiomyoma?

- slow-growing, benign tumour from **capsule or peripelvic tissues or renal vein**
 - usually small and appearance on imaging is variable } cystic to solid
 - can enhance and so is difficult to differentiate from RCC
 - **capsular origin suggestive but NOT diagnostic**
 - spindle cells with rare mitoses and no pleomorphism
 - consider leiomyosarcoma if increased mitotic rate or high pleomorphism
 - **+ve stain for smooth muscle on histology** } **+ve for keratin if sarcomatoid RCC**
- Rx → Rad Nx for large lesions
→ PNx if small, exophytic, and seems capsular

What other benign renal tumours have been described?

- fibroma } usually small
 - lipoma } usually large and can resemble AMLs (fat-rich AML)
 - hemangioma
 - lymphangioma } female predominance
 - reninoma } **from JG cells**
 - } stains +ve for factor 8 & factor 8-related Ag's
 - } get **HTN, hypoK, polydypsia, polyuria, H/A's**
 - } more common in F
- Rx → surgical excision

*** **pseudotumour (column of Bertin) → central lesion in solitary kidney** } **MAG3 to confirm*****

RENAL CELL CARCINOMA

Incidence and Etiology

What is the epidemiology of RCC?

- 2-3% of all adult malignancies
- M predominance (3:2)
- presents in 50's and 60's
- higher incidence in Blacks
- **mostly sporadic, only 4% familial**
- increasing incidence } increasing imaging
- **mostly incidental findings } despite this, increased incidence of advanced tumours with increased overall mortality rate**
- RCC in younger patients tends to be papillary, locally advanced, and high-grade
 - better survival, stage-for-stage
 - just as common as Wilms' tumour by 2nd decade

What type of cell are RCCs derived from?

- clear cell → PCT
- papillary → PCT
- chromophobe → intercalated cells of CD (distal CT)
- collecting duct → CD

What are the RFs for RCC?

- **smoking** } ~ 2-fold
- } dose & duration related
- **ESRD**
- long-standing obesity
- low SES
- urban living
- factory workers
- trichloroethylene exposure
- HTN
- radiation
- survivor of Wilm's tumour
- family hx of RCC

What is the principle of Knudson's hypothesis regarding familial forms of cancer?

- "2-hit hypothesis" } born with one abnormal allele of a tumour suppressor gene
- } 2nd hit required to form cancer
- all cells at risk } multicentric and early age of onset

What are the familial syndromes associated with RCC?

→ sporadic RCC more common } familial RCC accounts for ~4% only

→ all have AD inheritance pattern

1) VHL → clear cell RCC } most common

→ deletion of **3p25-26** } **VHL tumour suppressor gene**

- lack of VHL leads to loss of ubiquitin-mediated **HIF-1 α** down-regulation
- \uparrow 'd HIF-1 α protein in cell **upregulates VEGF**

→ HIF also upregulates **TGF α** , **PDGF**, **Glut-1 transporter**, **epo**, **CA-9**

→ early onset of BILATERAL & MULTIFOCAL RCC

→ type 1 (no pheochromocytomas) & type 2 (+ pheochromocytomas)

→ **manifestations include (organs that tubularize by day 21):**

- RCC (~50%) } most common cause of death from VHL
- renal cysts (~40%)
- benign retinal angiomas (~60%) } **earliest finding**
- benign CNS hemangioblastomas (~60%) } usually cerebellar or spine
 } **most common finding**
- pheochromocytomas (~20%)
- pancreatic cysts (~45%)
- pancreatic neuroendocrine tumours (islet cell)
- epididymal cystadenomas (~20%)
- endolymphatic sac tumours (~10%)

2) Hereditary papillary RCC → type 1 papillary RCC } least common familial syndrome
(HPRCC) → trisomy of 7q31 } C-met proto-oncogene

- increased production of *met* tyrosine kinase receptor
- upregulates hepatocyte growth factor (scatter factor) activity which results in proliferation of cells

→ onset during 40's with BILATERAL & MULTIFOCAL RCC

→ **NO extrarenal manifestations**

→ generally LESS AGGRESSIVE

3) Familial leiomyomatosis (HLRCC) → **type 2 papillary RCC** } can also get collecting duct RCC
→ **chromosome 1q42** } **tumour suppressor gene**

[illegible]

→ early onset with usually **SOLITARY & UNILATERAL RCC**
(unlike most hereditary & most papillary RCC tumours)

→ generally VERY AGGRESSIVE

→ **manifestations include:**

- RCC } only 20%
- cutaneous leiomyomas (painful) } ~100%
- uterine leiomyomas } ~100%

4) Birt-Hogg-Dube → usually **chromophobe RCC** or **clear cell RCC**

→ chromosome 17p11 } BHD-1 tumour suppressor gene

→ fibricillin protein (involves mTOR)

→ early age of onset and usually **BILATERAL & MULTIFOCAL**

→ **manifestations include:**

- RCC (only ~20-30%)
- renal oncocytoma
- lung cysts + spontaneous pneumothoraces
- skin fibrofolliculomas (painless)

What chromosomal abnormalities are associated with clear cell RCC?

- VHL 3p25
- p53 tumour suppressor gene
- PTEN/Akt pathway
- candidate tumour suppressor gene has also been described } 3p12

Tumour Biology and Clinical Implications

What evidence exists that RCC is immunogenic?

- 1) expression of tumour-associated antigens
 - CA-9 → aka MN-9
 - ~80% of RCCs (mostly clear cell)
 - expression normally inhibited by VHL protein
 - recognized by G250 monoclonal Ab
 - PRAME
 - RAGE-1
 - MUC-1
 - gp47
 - 2) isolation of tumour-associated immune cells
 - natural killer cells
 - cytotoxic and helper T cells
 - dendritic cells
 - 3) spontaneous tumour regression (uncommon)
 - most reported cases after cytoreductive Nx
 - 4) prolonged disease stabilization after immunotherapy
 - 5) durable responses to immunotherapy
- \ response rates typically
/ only ~15-20%

Why is RCC chemo-resistant?

- **expression of multidrug resistance (MDR) proteins**
 - MDR-1 (aka P-glycoprotein) is found in 90% of RCC
 - MDR-1 is an efflux pump that actively exports hydrophobic compounds eg. chemo

Why is RCC such a vascular tumour?

- upregulation of VEGF in RCC (especially clear cell)
 - VEGF is primary angiogenesis inducer
- upregulation of other angiogenic factors
 - } TGF- β 1
 - } angiogenin
 - } IL-8
 - } hepatocyte growth factor

What are the potential advantages of anti-angiogenic therapy?

- tumour control via anti-angiogenesis
- less likely to induce secondary malignancies } targets stable not genetically unstable cells
- less likely to have tumour resistance } targets stable cells
- synergistic with other anti-angiogenic agents & cytotoxic therapies

What other clinical implications are related to tumour biology?

- poor outcomes associated with INCREASED:
 - PCNA or **Ki-67 staining** } measure of proliferative index
 - erbB-2 staining } proto-oncogene
 - EGFR staining } receptor that promotes proliferation
 - MAP kinases, **Ras** } aberrant signal transduction
 - IGF, Bcl-2, telomerase activity } growth regulation factors
 - hepatocyte growth factor and its receptor (*met* proto-oncogene) } cell proliferation
 - proteases (eg MMPs) } cell differentiation
- poor outcomes associated with DECREASED:
 - **E-cadherin** and cadherin-6 } mediates adhesion between cancer cells,

Pathology

What does RCC look like on gross pathology?

- round to ovoid
- **2-4% are bilateral** \ **more common in familial RCC**
- **10% are multicentric** / (except familial leiomyomatous RCC)
- circumscribed by pseudocapsule of compressed parenchyma } not true capsule
- most are not grossly infiltrative } except collecting duct RCC and sarcomatoid variants
- yellow, tan, or brown
- cystic degeneration in 10-25% } better prognosis
- **calcification in 10-25%**
- frank invasion of collecting system or renal capsule in 20% } poor prognosis
- **venous thrombus in 5-10%**

What are the different histologic subtypes of RCC (CHART)?

1) conventional } 70-80%

- deletion of **3p25**
- mutated VHL tumour suppressor gene
- **clear cell, granular, and mixed types**
 - clear cells look “clear” due to cytoplasm **rich in glycogen, fat & cholesterol**
- **heterogeneous, yellow, with hemorrhage on gross** } hypervascular, often aggressive
- may respond to immunotherapy
 - might now be considered better prognostic subtype
- **von Hippel-Lindau syndrome is familial form**
- from PCT

2) papillary (chromophilic) } 10-15%

- trisomy of **7 and 17**
- abnormality of *met* proto-oncogene
- type 1 more likely multi-focal & type 2 worse prognosis (particularly type 2b)
- **homogeneous, white on gross**
- usually **hypovascular, multicentric**, variable prognosis
- **HPRCC (type 1), HLRCC (type 2) are familial forms**
- **ESRD/ARCD (type 1)**
- from PCT

3) chromophobe } 3-5%

- loss of chromosomes 1, 2, 6, 10, 13, 17, 21
- **classic vs eosinophilic type**
- **homogeneous, brown on gross**
- usually better prognosis but some aggressive variants exist
- **Birt-Hogg-Dube is familial form (chromosome 17)**
- from **intercalated cells of CD**

4) collecting duct } 1%

- aka Bellini's duct
- loss of chromosomes 1, 6, 8, 11, 18, 21, and Y
- gain of chromosomes 7, 12, 17, 20
- **medullary cell variant**
 - common in Blacks in their 30s w/ **sickle cell TRAIT** } **WORST PROGNOSIS**
 - from renal papillae
- centrally located, infiltrative, poor prognosis
- may respond to chemo
- from **medullary CD**

5) unclassified } 1%

- poorly defined
- poor prognosis
- **undefined cell of origin**

***** SARCOMATOID VARIANT of each subtype exists and are considered poorly differentiated tumours that carry a poor prognosis ****

What is the Fuhrman grading system for RCC (CHART)?

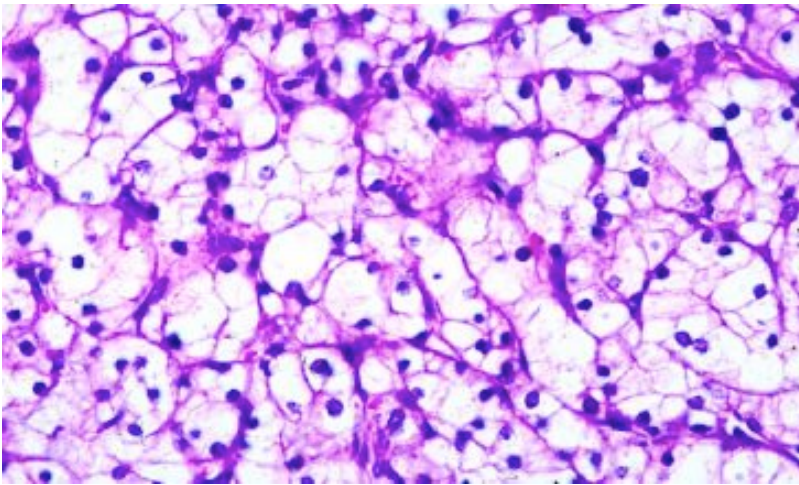
→ WAS ORIGINALLY CREATED FOR CONVENTIONAL CLEAR CELL TYPE (Susan Fuhrman)

GRADE	NUCLEAR SIZE (mm)	NUCLEAR OUTLINE	NUCLEOLI
1	10	round/oval	absent or inconspicuous
2	10-15	irregular	small
3	15-20	irregular	large
4	>20	bizarre	large with chromatin clumps

What are the histologic features of each subtype of RCC?

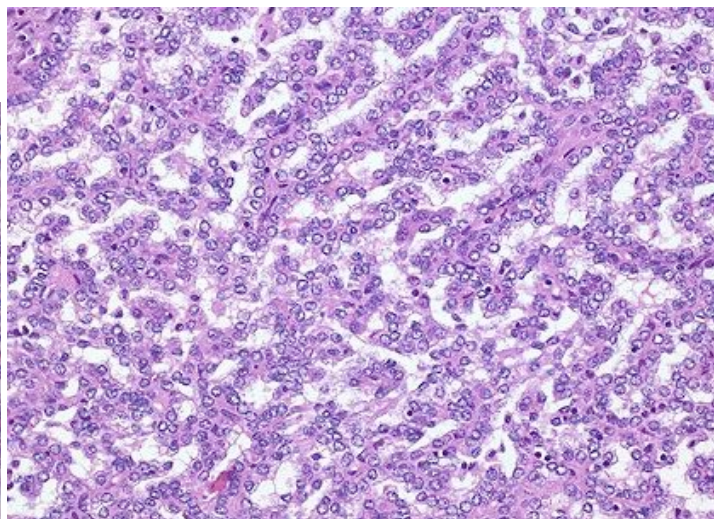
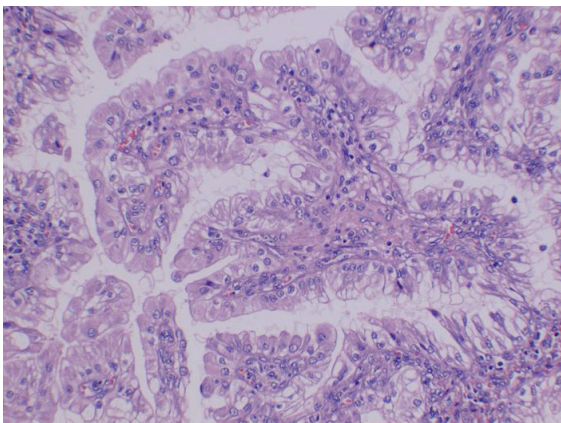
1) CONVENTIONAL

- clear cell → round cells with **abundant cytoplasm (rich in glycogen, fat, cholesterol)**
- granular → eosinophilic cytoplasm with abundant mitochondria (NOT so clear)



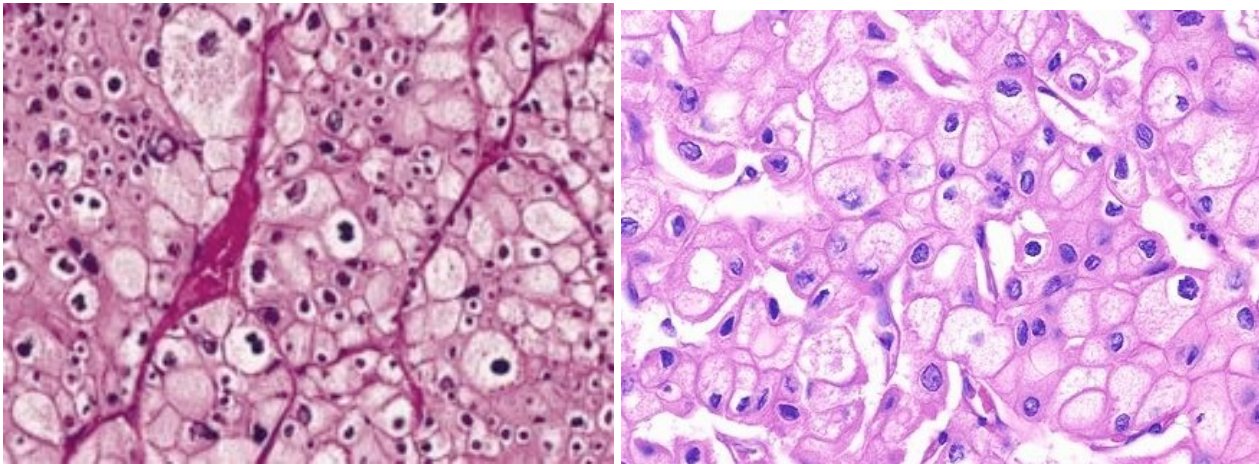
2) PAPILLARY (chromophilic)

- type 1 → basophilic cells (pink) + scant cytoplasm
- type 2 → eosinophilic cells (purple) + abundant cytoplasm
- papillary or tubular configuration } look for “foamy” histiocytes (white bunches) in type 1



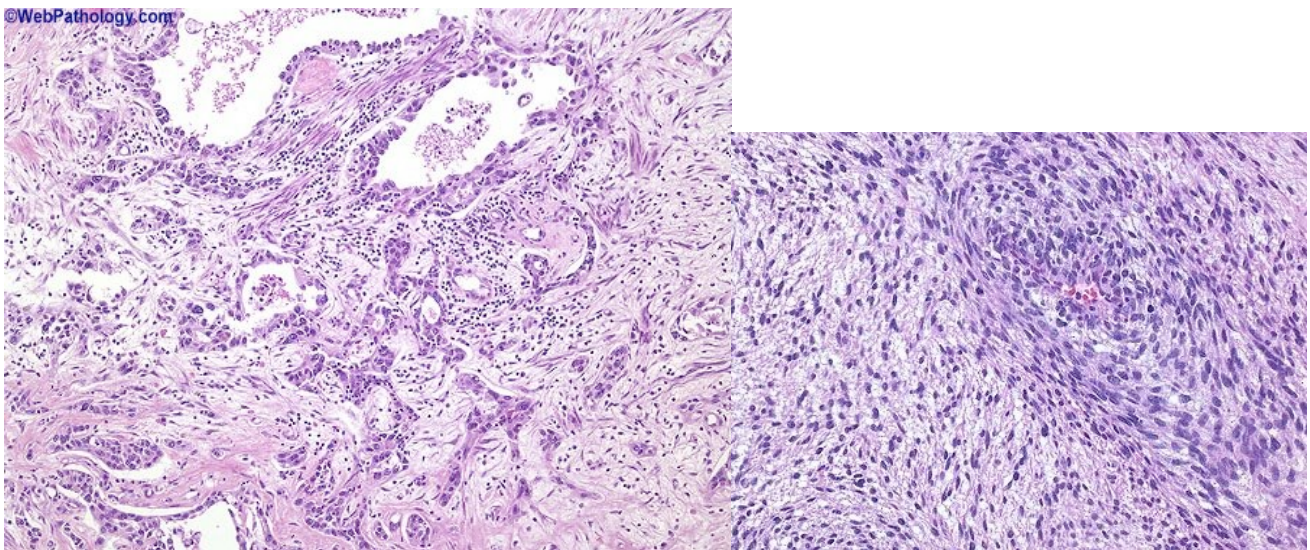
3) CHROMOPHOBE

- transparent cytoplasm with **reticular “plant cell” pattern with thick cell walls**
- **peri-nuclear halo**
- eosinophilic variants (30%)
- multiple **microvesicles on EM** that stain +ve for Hale’s colloidal iron
→ oncocytoma is Hale’s -ve
- **negative for vimentin**



4) COLLECTING DUCT

- admixture of dilated tubules & papillary structures lined by single layer of cuboidal cells
- **cobblestone appearance**



5) SARCOMATOID VARIANT

- spindle cell histology
- **stains +ve for vimentin**

Clinical Presentation

How does RCC present?

- **>50% are incidental**
- local tumour growth } palpable mass
 - } R-sided varicocele
 - } lower limb edema
- hemorrhage } flank pain
 - } gross hematuria
- **paraneoplastic syndrome } found in 20%**
 - **↑'d ESR (most common finding – 55%)**
 - **HTN (38%)**
 - **anemia (36%)**
 - **cachexia (35%)**
 - fever (17%)
 - non-metastatic hepatic dysfunction (Stauffer's syndrome) (15%)
 - hyperCa } **only feature that responds to medical Rx**
 - polycythemia (epo)
 - neuromyopathy
 - amyloidosis
 - Cushing's
- metastatic } constitutional symptoms (wt loss, night sweats)
 - } lymphadenopathy
 - } bone pain
 - } cough
 - } hypercalcemia (nausea, fatigue, anorexia, decreased DTRs)

List 8 compounds that RCC can produce?

- PTH-like peptide
- Vit D₃
- Epo
- renin
- PGs
- HCG
- insulin
- cytokines and inflammatory mediators

List causes of HTN in patients with RCC.

- 1) renin secretion
- 2) RAS from compression
- 3) compression of ureter
- 4) AVF

What is the cause of hyperCa in RCC?

- 1) PTH-like peptides
- 2) Vit D₃
- 3) PGs
- 4) osteolytic bone mets

What is the management of hyperCa?

- 1) hydration followed by lasix diuresis
 - stop any thiazides (↑'s Ca reabsorption)
- 2) bisphosphonates (eg zoledronic acid 4mg iv q4wks)
- 3) steroids
- 4) calcitonin

What is Stauffer's syndrome?

- **paraneoplastic syndrome of non-metastatic hepatic dysfunction associated with RCC**
- found in 5-20% } resolves in 60-70% after nephrectomy
- **mediated by IL-6**
- **↑'d LFTs, ALP, PTT, bili**
- **↓'d WBC, albumin**
- must r/o hepatic mets

Screening and Clinical Associations

Why do we not screen the general population for RCC?

- low incidence → ~1 in 10,000
- high prevalence of benign renal tumours → leads to unnecessary tests and Rx

Which target populations SHOULD be screened for RCC?

- 1) ESRD (5-20 fold higher risk of RCC)
 - if long life expectancy and no major comorbidities
 - periodic U/S or CT starting 3rd yr on dialysis
 - periodic screening even after renal Tx
- 2) VHL patients
 - biannual CT or U/S starting at age 11yrs
 - periodic screening for systemic manifestations } ophtho, neuro, etc
- 3) relatives of VHL patients
 - get genetic counseling and screen for VHL
 - if +ve, as above
 - if -ve, less stringent f/u
- 4) relatives of patients with HPRCC, HLRCC, etc
 - consider genetic counseling
 - periodic U/S or CT
- 5) Tuberous Sclerosis
 - 2% risk of RCC
 - periodic screening with U/S or CT
 - for small risk of RCC and for AMLs

*** **AD PCKD warrants NO screening** ***

What are the NIH recommendations for VHL?

- 1) annual P/E and eye check starting as infant
- 2) periodic hearing test starting as infant
- 3) urinary catecholamines at 2yrs old then q1-2yrs
- 4) MRI of CNS q2yrs starting at age 11
- 5) abdo/pelvis U/S annually starting at age 11
 - CT q6/12 if cysts or tumours develop

List renal complications of ARCD in ESRD patients

- RCC (papillary most common)
- hematuria
- renal cortical adenoma
- recurrent infection/abscess

What is Tuberous Sclerosis?

- AD inherited disorder
- **mental retardation**
- renal cysts
- renal AMLs
- pheochromocytoma
- **epilepsy**
- hamartomas
- **skin adenoma sebaceum (facial angiofibromas – reddish spots or bumps)**
- ungual or subungual (nails) fibromas
- ash leaf spots (white spots)
- Shagreen patch
- intracranial subependymal nodules
- lung lymphangiomyomatosis
- cardiac rhabdomyomas

Staging and Diagnosis

Describe the Robson staging of RCC.

- didn't differentiate between size of RCC when confined to kidney
- stage 3 } LN mets considered same as venous thrombus
 - } extent of nodal & venous involvement not delineated
- Stage I: tumour within renal capsule
- Stage II: tumour invasion of perinephric fat (confined to Gerota's)
- Stage III: tumour involvement of regional LN and/or renal vein and IVC
- Stage IV: adjacent organs or distant mets

What is the TNM staging system of RCC (2002)?

- 1) T → TX – can't assess primary
 - To – no primary
 - T1a – tumour <4cm and confined to kidney
 - T1b – tumour 4-7cm and confined to kidney
 - T2 – tumour >7cm and confined to kidney
 - T3a – tumour invades adrenal or perinephric fat but NOT outside Gerota's
 - T3b – tumour extends into segmental veins, renal vein, or IVC below diaphragm
 - T3c – tumour extends into IVC above diaphragm or invades wall of IVC
 - T4 – tumour invades beyond Gerota's
- 2) N → NX – can't assess LNs
 - No – no regional LNs
 - N1 – mets to single regional LN
 - N2 – mets to >1 regional LN
- 3) M → MX – can't assess
 - Mo – no mets
 - M1 – mets
- 4) Stage grouping
 - stage I T1 No Mo
 - T2 No Mo
 - T1 or T2 N1 Mo
 - T3 No or N1 Mo
 - T4 or N2 or M1

- RCC <4cm do significantly better (Frank et al. J Urol '04 p1652)
- 7cm was mean tumour size in SEER database
- invasion of renal sinus fat (T3a) may in fact be worse than venous thrombus (T3b/c)
- adrenal extension (T3a) should likely be classified as T4
- indirect adrenal involvement (T3a) might be better classified as M1

Table 47-14 -- TNM Stage and 5-Year Survival for Renal Cell Carcinoma

Findings	Robson Stage	TNM (2002)	5-Year Survival (%)
Organ confined (overall)	I	T1-2 N0 M0	70-90
(≤4.0 cm)	I	T1a N0 M0	90-100
(>4.0 cm, ≤7.0 cm)	I	T1b N0 M0	80-90
(>7.0 cm)	I	T2 N0 M0	70-80
Invasion of perinephric fat	II	T3a N0 M0	60-80
Adrenal involvement	II	T3a N0 M0	0-40
Venous involvement	IIIA	T3b-c N0 M0	40-60
Locally advanced	IVA	T4 N0 M0	0-20
Lymphatic involvement	IIIB	any T, N+ M0	0-20
Systemic metastases	IVB	any T, any N, M1	0-10

What is the staging w/u of a renal mass suspicious for RCC?

- 1) **Hx and P/E** } symptoms – hematuria, bone pain, wt loss, poor performance status, etc
 } palpable mass, lower extremity edema, nonreducing varicocele, etc
- 2) Lab work } **CBC, lytes, creat, LFTs, ALP, Ca profile, ESR**
 } urine cytology (if suspicious for TCC)
- 3) Imaging } **biphasic CT abdo/pelvis**
 } **CXR**
 } +/- chest CT (if abN CXR or if pulmonary symptoms)
 } +/- MRI (if locally advanced tumour, possible venous involvement, renal dysfunction, or
 if allergy to contrast)
 } +/- bone scan (if elevated ALP, if bone pain, if ECOG status ≥ 1)
 } +/- PET scan (good specificity for mets if +ve)

What are the findings suggestive of ipsilateral adrenal involvement (T3a)?

- 1) enlarged gland on CT
- 2) upper pole tumour
- 3) extensive malignant replacement of kidney
- 4) palpably abnormal adrenal during OR

What is the management of small hilar nodes seen on CT?

- nodes >2cm are almost always RCC → Bx or frozen section during OR
→ most will benefit from Radical Nx either way
- most nodes <2cm are inflammatory/reactive and shouldn't preclude Radical Nx

What are the CT findings suggestive of renal vein involvement?

- can see ~80% of renal vein thrombi } most false -ves are on R side (short vein)
- can see 95% of IVC thrombi
- 1) venous enlargement
- 2) abrupt change in caliber of vein
- 3) intraluminal areas of ↓'d density or filling defects
- 4) presence of collateral vessels

What are CT angio findings suggestive of extra-capsular spread of RCC ?

- all not reliable
- 1) discrete mass in peri-nephric space (best)
- 2) stranding or cob-webbing in peri-nephric space
- 3) collateral vessels
- 4) fat obliteration
- 5) fascial thickening

What is the best test to assess an IVC thrombus?

- MRI is best test } multiplanar CT may also be good
- venacavography is reserved for equivocal MRI/CT or contraindication to MRI

What is the role of FNA or Perc Bx?

- → limited role } **GROWING INDICATIONS**
- imaging is quite accurate (~80-90%)
- sampling error } **PRETTY LOW NOW**
- eosinophilic variants of RCC very similar to oncocytoma given limited tissue
- sensitivity and specificity ranges from 80%-95%
- has inherent risks
- **YES to rule out infection/abscess, lymphoma, mets (lung, breast, colon, melanoma)**

What are the potential complications of renal Bx?

- bleeding
- infection
- AVF
- pneumothorax
- bowel perf
- seeding (5 reported cases only)

Prognostic Factors

What are the important prognostic factors for RCC (CHART)?

- 1) clinical signs or symptoms
 - symptomatic presentation
 - wt loss >10% of body weight
 - **poor performance status (ECOG)**
 - paraneoplastic syndromes
 - short mets-free interval
- 2) tumour-related factors
 - **pathological stage** } **single MOST IMPORTANT prognostic factor**
 - tumour size (independent of stage)
 - **Fuhrman nuclear grade** } Fuhrman 1 and 4 are significant
 - } Fuhrman 2 and 3 are similar
 - only really applies to clear cell RCC
 - **histologic subtype** } ?clear cell now considered better than papillary or chromophobe
 - } collecting duct, medullary variant & sarcomatoid variants bad
 - site and burden of mets } brain is very bad
 - tumour necrosis
 - DNA ploidy } diploid better than non-diploid tumours
- 3) lab findings
 - anemia
 - hyperCa
 - elevated ESR
 - low CA-9 } VHL-types (high CA-9) do better than VHL-independent pathogenesis
 - thrombocytosis
 - elevated ALP
 - increased proliferative factor Ki-67

***** on multivariate analysis, the 3 best prognostic factors were TNM stage, performance status, and tumour grade (Zisman et al J Clin Oncol 2001) *****

What factors are included in the Kattan prognostic nomogram for RCC?

- '97 pathologic stage
- histologic subtype
- presence of symptoms
- tumour size

What is the prognosis of patients with M+ RCC?

- **1yr survival <50%**
- 10yr survival <5%
- synchronous mets worse
- for asynchronous mets, disease-free interval is key
- visceral or retroperitoneal LN mets particularly bad
- lung-only mets particularly good
- **cytoreductive Nx may improve survival (Flanigan et al. J Urol '01) } 7 month benefit**

TREATMENT OF LOCALIZED RCC

Radical Nephrectomy

What are the basic principles of a Radical Nx?

- 1) early ligation of renal vessels
- 2) excision of kidney outside Gerota's fascia
→ **25% of localized RCCs have perinephric fat involvement**
- 3) excision of ipsilateral adrenal
→ not always necessary
- 4) complete regional lymphadenectomy from crus of diaphragm to aortic bifurcation
→ not always necessary (controversial)

What are the indications for excision of ipsilateral adrenal?

- 1) enlarged adrenal on imaging
- 2) abnormal adrenal gland on palpation
- 3) upper pole tumour
- 4) locally advanced tumour
- 5) tumour that displaces the kidney significantly

What are the arguments AGAINST extensive regional lymphadenectomy?

- mets via bloodstream seen with equal frequency as lymphatics
- lymphatic drainage of the kidney is variable
- even if more accurate staging, no good form of adjuvant systemic therapy anyways

What are the arguments FOR extensive regional lymphadenectomy?

- gives prognostic information
- may cure subset of patients with micromets in regional LNs } <2-3%
- beneficial in setting of cytoreductive Nx
→ better than if LNs not removed (Pantuck et al '03)

What are the RFs for lymphatic involvement with RCC?

- Blute et al '04
- high grade
- stage \geq pT3
- tumour necrosis on histology
- tumour size >10cm

What factors determine the approach to a Radical Nx?

- size of tumour
- location of tumour
- patient body habitus
- previous surgery
- laparoscopic } transperitoneal \ faster recovery, less pain,
 } retroperitoneal / comparable cancer control
- open
 - transperitoneal } flank
 - } extended subcostal
 - } chevron → tumour thrombus
 - } thoracoabdominal → large tumours
 - retroperitoneal } flank → limited exposure if large tumour or difficult hilum

What features would deter you from Lap Nx?

- tumour >10cm
- evidence of local invasion
- renal vein involvement
- lymphadenopathy
- difficult hilar dissection
- large abdominal wall hernia
- patient preference
- need for ancillary procedures

What is the recommended f/u regimen after Radical Nx for localized RCC?

→ depends on stage of RCC

- History & Physical
- Lab work (CBC, lytes, creatinine, Ca, ALP, LFTs)
- Imaging (CXR, abdo U/S or CT)
 - bone scan, CT head, etc only if localized symptoms

Table 47-16 -- Postoperative Surveillance after Radical Nephrectomy for Localized Renal Cell Carcinoma

Pathologic Tumor Stage	History, Examination, and Blood Tests	Chest Radiograph	Abdominal CT Scan
T1 N0 M0	Yearly	—	—
T2 N0 M0	Yearly	Yearly	Every 2 years
T3a-c N0 M0	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At 1 year, then every 2 years

What are the CUA recommendations for f/u after Radical Nx for RCC? (CUA Guidelines '08)

→ pT1

- Hx, Physical, Bloodwork (CBC, lytes, creat, LFTs) } at 1yr then q1yr
- CXR } at 1yr then q1yr
- abdo CT or U/S } at 2yrs & 5yrs

→ pT2

- Hx, Physical, Bloodwork } q6months x 3yrs then q1yr
- CXR } q6months x 3yrs then q1yr
- abdo CT or U/S } at 1yr, 3yrs & 5yrs

→ pT3

- Hx, Physical, Bloodwork } q6months x 3yrs then q1yr
- CXR } q6months x 3yrs then q1yr
- abdo CT } q6months x 2yrs then at 3yrs & 5yrs

→ pTxN+

- Hx, Physical, Bloodwork } at 3months, 6months, then q6months x 3yrs, then q1yr
- CXR } at 3months, 6months, then q6months x 3yrs, then q1yr
- CT abdo } at 3months, 6months, then q6months x 3yrs, then q1yr

What is the risk of LOCAL recurrence after Radical Nx for Localized RCC?

- ~**2% local recurrence rate**
 - RFs are T stage & LN +ve disease
- 60% of local recurrences have evidence of mets also

What is the recurrence-free survival data for Radical Nx?

- 5 yr survival rates of ~90% for stage I
- 5 yr survival rates of ~75% for stage II
- 5 yr survival rates of ~60% for stage III

What are the potential complications after radical nephrectomy?

→ 20% post-op complication rate

→ 2% operative mortality rate

- 1) systematic
 - MI - CVA - PE
 - CHF - DVT - ARF
- 2) GI system
 - bowel injury - pancreatic injury (tail for L Radical Nx)
 - duodenal injury - SBO or LBO
 - liver lacerations (for R Radical Nx) - ileus
 - splenic injuries (for L Radical Nx) - incisional hernia
- 3) Pulmonary system
 - pneumothorax, tension pneumothorax
 - atelectasis
 - pneumonia
- 4) infections
 - wound infections
 - abscesses
 - lymphocele
- 5) local/incisional complications
 - incisional hernia
 - flank bulge (due to injury to intercostals nerve and muscle denervation)

Nephron-Sparing Surgery

Why has interest in PNx increased over the years?

- advances in renal imaging
- experience with renal vascular sx
- improved methods of preventing ischemic injury } 90% long-term preservation of renal fxn
- growing numbers of incidental small renal masses
- good long-term survival rates } 80-100% disease-specific 5yr survival

What are the classic indications for PNx for RCC?

- 1) if radical Nx would render patient anephric
 - bilateral RCC
 - RCC in solitary functioning kidney
 - 2) functioning contralateral kidney but systemic disease that threatens future renal function
 - stones - chronic pyelo
 - RAS - VUR
 - DM - nephrosclerosis
 - HTN
 - 3) single, small (<4cm), localized RCC with normal contralateral kidney } moving to <7cm
 - 4) syndromic RCC (eg VHL)
 - 5) renal dysfunction
 - 6) select cases of Wilm's tumour or upper tract TCC
- size of margin doesn't matter (Sutherland et al '02)
- need at least 20% of one renal unit to avoid ESRD

What are the contraindications for Partial Nx?

- 1) tumour >4cm (may be changing now)
- 2) tumour suggestive of renal TCC
- 3) difficult central tumour
- 4) +ve LNs
- 5) renal vein or IVC thrombus

What is the w/u prior to PNx?

- r/o locally extensive disease
- r/o mets
- delineate relationship of tumour to intrarenal vascular supply and collecting system
→ urine cytology if central tumour suspicious for TCC

What are the basic principles of Partial Nx for malignant disease?

- vascular control
- avoidance of ischemic renal damage
- complete tumour excision with free margins
- precise closure of collecting system
- careful hemostasis
- closure or coverage of renal defect

What are the indications for “ELECTIVE” PNx?

- unilateral
- unifocal
- small tumour (<4cm)
- patient wishes
→ cancer-specific survival 90-100% } similar to Radical Nx
→ location (peripheral vs central) NOT significantly different

What are the potential benefits of an elective PNx?

- lesion could be benign } ~20%
- ESRD is slightly less common then after Radical Nx

What is the risk of ESRD after PNx?

- if >50% reduction in renal mass, at risk of long-term renal dysfxn from hyperfiltration injury
- proteinuria \
- FSGS } try to prevent/slow via diet (low-protein) & meds (ACEi)
- progressive renal failure /

What is the recommended f/u regime after PNx for localized RCC?

→ depends on stage & size of RCC

- History & Physical
- Lab work (CBC, lytes, creatinine, Ca, ALP, LFTs)
→ urinary protein if significant reduction in renal mass
- Imaging (CXR, abdo U/S or CT)
→ bone scan, CT head, etc only if localized symptoms

What are the CUA recommendations for f/u after Partial Nx for RCC? (CUA Guidelines '08)

→ pT1

- Hx, Physical, Bloodwork (CBC, lytes, creat, LFTs) } at 1yr then q1yr
- CXR } at 1yr then q1yr
- abdo CT or U/S } at 2yrs & 5yrs

→ pT2

- Hx, Physical, Bloodwork } q6months x 3yrs then q1yr
- CXR } q6months x 3yrs then q1yr
- abdo CT or U/S } at 1yr, 3yrs & 5yrs

→ pT3

- Hx, Physical, Bloodwork } q6months x 3yrs then q1yr
- CXR } q6months x 3yrs then q1yr
- abdo CT } q6months x 2yrs then at 3yrs & 5yrs

→ pTxN+

- Hx, Physical, Bloodwork } at 3months, 6months, then q6months x 3yrs, then q1yr
- CXR } at 3months, 6months, then q6months x 3yrs, then q1yr
- CT abdo } at 3months, 6months, then q6months x 3yrs, then q1yr

Table 47-18 -- Postoperative Surveillance after Partial Nephrectomy for Localized Renal Cell Carcinoma

Pathologic Tumor Stage	History, Examination, and Blood Tests	Chest Radiograph	Abdominal CT Scan
T1 N0 M0[*]	Yearly	—	—
T2 N0 M0[*]	Yearly	Yearly	Every 2 years
T3 N0 M0	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then every 2 years

* Based on 1997 AJCC classification system, with T1 \leq 2.5 cm and T2 > 2.5 cm.

How common is local recurrence after PNx?

→ **stage dependent } 2-10% recurrence rate**

- usually found distant from tumour bed
- likely due to unrecognized microscopic multifocal RCC
- associated with +ve surgical margins, multifocality, grade

What is the management of renal masses in VHL?

- observation recommended **until lesion is >3cm (NCI)**
- excision of all solid & cystic renal lesions
- use of intra-op U/S may pick up additional tumours } ~25%
- options are: 1) partial Nx (1st line)
- 2) bilateral Radical Nx + renal replacement therapy
- ~27% local recurrence rate (vs 2-10% for sporadic RCC)

What are the potential complications after a Partial Nx?

- overall rate <5%
- intra-op
 - hemorrhage
 - adjacent organ injury
 - ureteral injury
 - pleural injury
- early post-op
 - urinoma/urinary fistula
 - pneumothorax
 - delayed bleeding
 - ureteral obstruction (clots)
 - ileus, SBO
 - MI/DVT/PE
 - infection
- late post-op
 - AV fistula
 - renal insufficiency (permanent in <5% of solitary kidneys after PNx)
 - ureteral stricture
 - hernia
 - HTN

What are the RFs for development of a urinary fistula?

- central tumours
- size >4cm
- need for major reconstruction of collecting system
- extracorporeal surgery

What are the indications for Partial Nx for benign disease?

- 1) hydronephrosis with atrophy or atrophic pyelo in a duplicated renal segment
- 2) calyceal diverticulum complicated by infection or stones
- 3) stone disease with obstruction of LP calyx or segmental parenchymal disease w/ impaired drainage
- 4) renovascular HTN due to segmental parenchymal damage or non-correctable branch renal artery dz
(rare now given advances in renovascular reconstruction)
- 5) traumatic renal injury with irreversible damage to a portion of the kidney
- 6) benign tumours (AML, oncocytoma)

Thermal Ablative Therapies

What are the indications for thermal ablation therapy?

- advanced age
- significant comorbidities
- patient with local recurrence after previous PNx
- hereditary RCC (VHL, HPRCC, Birt-Hogg-Dube, etc)
- patient wishes and amenable to nephron-sparing surgery

What are the principles of cryoablation?

- 1) rapid freezing } **cell death at temp lower than -20°C**
 - 2) gradual thaw
 - 3) repetition of freeze-thaw cycle
 - 4) ice ball extended ~1cm beyond margin of tumour
- laparoscopic or percutaneous
- local recurrence represented by enhancement } **~5-10% recurrence rate**
- may be underestimation because some SRMs are benign } most studies don't have pathology

How does cryoablation work?

- involves **immediate cellular damage & delayed microvascular failure**
- cells lose fluid and become dehydrated/dessicated
 - intracellular ice forms afterwards
 - vasoconstriction, endothelial cell damage causes porous vessel walls, interstitial edema, platelet aggregation, microthrombi, vascular congestion
 - cryoablated area becomes ischemic

What are the principles of RFA?

- 1) irreversible cellular damage >45°C
 - 2) immediate cell death >60°C
 - 3) thermal ablation of ~4cm
- local recurrence represented by enhancement } **10% recurrence rate**

How does RFA work?

- involves **denaturation of intracellular proteins & melting of cellular membranes**

What are the advantages of cryotherapy over RFA?

- can visibly see "ice ball" in real time to assess ablative region
- possibly more reliable tumour kill with cryo

What are the potential complications of ablative therapy?

- acute renal failure
- UPJ strictures
- necrotizing pancreatitis
- lumbar radiculopathy
- failed therapy
- bowel injury
- fistula

Observation

What are the indications for observation of small renal masses?

- advanced age
 - significant comorbidities
 - patient wishes } for small (<3cm), well-marginated, homogeneous lesions
 - } serial imaging q6 or 12 months
- **growth rate is ~3-4mm per year**

What are the criticisms of the data supporting observation of small renal masses?

- many small renal masses may be benign (makes data look better)
- growth rate was calculated retrospectively } selection bias
- there exists a subpopulation of patients with rapidly growing masses

TREATMENT OF LOCALLY ADVANCED RCC

IVC involvement

What are the clinical signs & symptoms suggestive of an IVC thrombus?

- **RCC + venous thrombus on presentation occurs in 4-10%**
- “MAP a PLAN for the Vein”
- Murmur in R atrium (mass)
 - Abdo veins (superficial) dilated
 - PE
 - Proteinuria
 - Lower limb edema
 - Ascites
 - Non-functioning kidney
 - Varicocele on R side, or one that doesn't collapse with recumbency

What is the staging of the level of the IVC thrombus?

- stage I } adjacent to the os of the renal vein
 → use Satinsky clamp on IVC
 - stage II } infrahepatic
 → sequential clamping of distal IVC, contralateral renal vein, cephalad IVC, occlusion of any lumbar veins
 - stage III } involving the intrahepatic portion of the IVC but below the diaphragm
 → liver mobilization, exposure of intrahepatic IVC
 → may need to do Pringle maneuver (temporary occlusion of portal triad)
 - stage IV } supradiaphragmatic
 → cardiopulmonary bypass with circulatory arrest
- *** IVC wall invasion is worst prognosis ***
- resection of caval wall + reconstruction/grafting may be required
 - if chronic IVC occlusion, then no need to reconstruct IVC due to collateral formation

What imaging tests are used to evaluate venous thrombi?

- color flow abdominal Doppler
- CT angiogram
- TEE
- renal arteriography } can see vascularization of thrombus in 35-40% of cases
- } can embolize pre-operatively
- **MRI → preferred test } noninvasive and accurate**
- contrast venocavography } only for equivocal MRI or when MRI is contraindicated
- **coronary angiography performed if pt will need circulatory arrest; simultaneous CABG**

What is the mortality rate associated with Radical Nx + caval thrombectomy?

- 5-10% for upper level thrombi } patient health is a big factor

Locally Invasive RCC

How do patients with locally invasive RCC present?

- back pain } invasion of posterior abdominal wall, nerve roots, or paraspinous muscles
- compression into liver (but not usually invasion)
- extension into colon or its mesentery } often see parasitic vessels
- rarely see duodenal or pancreatic invasion } poor prognostic sign

What is the DDX of a large invasive upper quadrant abdo mass?

- adrenocortical carcinoma
- infiltrative TCC
- sarcoma
- lymphoma

What is the role of surgical resection of locally invasive RCC?

- en bloc resection of adjacent organs may be indicated as Sx is only effective management for RCC
- 5yr survival rate for pT4 is 5%
- consideration of pre-op embolization to facilitate dissection

What is the role of debulking surgery for locally invasive RCC?

- limited role } ~10% survival at 1yr after debulking partial resection

What is the role of RADs for locally invasive RCC?

- limited role } maybe for palliation of symptomatic local recurrence in non-Sx candidates
- no improved survival

Local Recurrence after Radical Nx or Partial Nx

What is the risk of local recurrence of RCC after Radical Nx?

- ~**2% of cases** } only 40% of local recurrences are isolated (most also have systemic mets)
- RFs for local recurrence after Rad Nx } high T stage
- } locally advanced disease
- } node +ve disease

What is the management of isolated local recurrence after Radical Nx?

- surgical resection indicated if no mets and patient suitable candidate for surgery
- long-term cancer-free status in ~30-40%
- en bloc resection of adjacent involved organs often required
- high risk of morbidity

What is the risk of local recurrence of RCC after Partial Nx?

- **2-5%** } most are distant from actual tumour bed
- probably result of unrecognized multicentricity or de novo occurrence NOT true Rx failure
- RFs for local recurrence after Partial Nx } advanced T stage & margin status

What is the management of isolated local recurrence after Partial Nx?

- repeat Partial Nx
- completion Nx
- thermal ablative therapies

What is the significance of local recurrence after thermal ablative therapy?

- ~5% for cryotherapy & ~10% for RFA } may be better due to benign tumours
 - usually represents treatment failure } recurrence in tumour bed
 - persistent enhancement within tumour bed
 Rx → repeat thermal ablative therapy VS completion N

Adjuvant Therapy for RCC

What are the indications for adjuvant therapy for RCC?

- 1) **distant mets** } ~ **25%**
- 2) **local recurrence** } ~ **5%**
- 3) research setting } neo-adjuvant, neo-adjuvant prior to cytoreductive Nx, adjuvant, etc

What have clinical trials shown regarding adjuvant therapy for RCC?

- endpoints include progression-free survival, time to progression, and overall survival
- most studies are underpowered to detect small differences in survival
- peri-op RADs } no survival advantage
- adjuvant progesterone } no survival advantage
- adjuvant autologous tumour vaccine preps (eg heat shock protein) } mostly negative results
- adjuvant cytokines (IL-2 and IFN α)
 - 4 RCTs (Porzsolt et al '92, Pizzocaro et al '01, Messing et al '03, Clark et al '03)
 - 3 with IFN α and 1 with IL-2
 - no improvement in DFS or overall survival } all histologic subtypes were included though
 - ~15-20% response rate
 - **high-dose IL-2 is only adjuvant Rx that may have possibility of CR (high morbidity)**
- adjuvant TKI's (sorafenib, sunitinib, etc)
 - ~30% response rates

TREATMENT OF METASTATIC RCC

Nephrectomy

How common is metastatic RCC?

- ~ **30% of patients have mets on presentation** } 50% lung, 33% liver, 30% bone, 25% brain
- 40-50% will develop mets after diagnosis

What are the indications for Nx in the setting of metastatic RCC?

- **6-7 month SURVIVAL BENEFIT**
- about 10-30% can't undergo systemic Rx due to post-op complications or rapid progression
- 1) severe bleeding
- 2) severe pain
- 3) paraneoplastic syndromes
- 4) compression of adjacent viscera
- 5) cytoreductive Nx
 - a) with adjuvant systemic therapy
 - spontaneous regression of mets } rare, approximately 1% (usually lung mets)
 - 2 RCTs (Flanigan et al '01 NEJM, Mickisch et al '01 Lancet)
 - **improved survival in Nx + IFN α group**
 - **median survival 14months vs 8 months**
 - **best for good ECOG status & if lung mets only**
 - b) in conjunction with resection of solitary met
 - c) in trial setting

What are the contraindications to cytoreductive Nx + systemic cytokine therapy AS PER MSK PROTOCOL?

- 1) advanced symptoms (ECOG ≥ 2)
- 2) mets in critical areas (CNS, SC compression)
- 3) major organ dysfunction
- 4) significant comorbid illnesses

What are the contraindications to cytoreductive Nx + systemic cytokine therapy?

- 1) ECOG >1
- 2) age >70yrs
- 3) >10% wt loss in last 6months
- 4) mets to brain, bone or liver
- 5) >1 metastatic site
- 6) metastatic disease burden > local disease burden
- 7) non-clear cell, sarcomatoid, or high grade pathology
- 8) ESR >70 mm/hr
- 9) LDH >280 IU/l
- 10) albumin <4 g/dL
- 11) neutrophils >7 kg/mm³
- 12) Hg <10.4 g/dL
- 13) inadequate pulmonary or cardiac reserves for immunotherapy

APPENDIX 1: ECOG PERFORMANCE STATUS

GRADE	ECOG
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

→ ECOG PERFORMANCE STATUS CLASSIFICATION

Hormonal Therapy

What is the role of hormonal therapy for metastatic RCC?

- **very limited role } response rate ~2%**
- medoxyprogesterone looked promising initially but found to be poor } maybe for palliation

Chemotherapy

What is the role of CHEMO for metastatic RCC?

- **RCC is chemo-resistant → very limited role (VINBLASTINE) } response rate <5%**
- due to expression of **MDR-associated protein** on surface of RCC cells
 - P-glycoprotein is an efflux pump that keeps intracellular chemo drug [] very low
- **may have role for sarcomatoid variants } doxorubicin, gemcitabine**

Radiation Therapy

What is the role of RADs for metastatic RCC?

- **limited role**
- used occasionally as adjuvant treatment after Radical Nx and for palliation of mets
 - no improvement in survival
 - **mainly of palliation of symptomatic bony mets & brain mets (+/-gammaknife)**
 - may now have role in combination with TKIs

Cytokines and Immunologic Therapy

What evidence supports the use of immunologic therapy for RCC?

- demonstration of T-cell infiltrates in tumour
- development of T-cell lines (CD8) with specificity for autologous tumour
- finding of tumour-associated antigens on RCC cells that are MHC restricted

How does IL-2 work?

- **T-cell growth factor → stimulates cytotoxic T-cells**
- can be given as iv bolus, continuous iv infusion, sc injection
 - **requires hospitalization & has high morbidity**
 - high-dose IL-2 schedule recommended due to better results } toxicity is high though
- overall response rate = ~15% } >20% if combined with IFN- α
- complete response rate = ~5%
 - **high dose IL-2 is only adjuvant Rx that has shown CR } high morbidity**
- limited demonstrable survival benefit
- S/Es } flu-like symptoms, vascular leak syndrome, pulmonary edema, peripheral edema

What is the vascular leak syndrome associated with IL-2 therapy?

- hypoTN + oliguria + organ failure
- Rx → needs aggressive hydration + hemodynamic monitoring

How does IFN α work?

- **pleiotropic protein with antiviral, immunomodulatory, and anti-proliferative activities related to modulation of gene expression in certain cell populations**
- overall response rate = ~12% } >20% if combined with IL-2
 - usually partial response only
- complete response only 2%
- improved median survival by ~4months
- S/E's } flu-like symptoms, depression, other neuropsych disorders

List factors predictive of poor response to immunotherapy (Motzer criteria)

- 1) poor performance status (Karnofsky <80)
- 2) mets-free interval <12 months
- 3) anemia
- 4) LDH >1.5x upper limit of normal
- 5) corrected Ca >10mg/dL
- 6) no Nx done

What are the survival rates of patients with metastatic RCC?

- poor risk (≥ 3 poor prognostic factors) → ~5month overall median survival
 - NOT CANDIDATE for CYTOKINE Rx
- intermediate risk (≤ 2 poor prognostic factors) → 14 month overall median survival
- favorable risk (no poor prognostic factors) → 26 month overall median survival

What is the role of targeted agents?

→ growth factors such as VEGF and PDGF bind to receptor tyrosine kinases that regulate cell proliferation and survival and can promote tumour-associated angiogenesis and growth

→ targeted therapy is aimed at inhibiting VEGF and PDGF pathways

1) bevacizumab

- **IgG1 monoclonal Ab** that binds to all VEGF isoforms } **sequesters circulating VEGF**
- longer time to progression (4.8 vs 2.5 mos) w/ 10mg/kg in cytokine-refractory RCC (Yang '03)

2) erlotinib

- **TKI that blocks EGFR pathway**
- when given with bevacizumab, additive anti-tumour effects seen (Rini et al '05)

3) sunitinib/sunitinib (SU11248) (od dosing)

- **TKI that inhibits VEGFR-2, PDGFR, c-Kit, and Flt3** \ **now considered as**
- partial response rates of ~40% (Motzer et al '04 and '05) / **1st line therapy**
- the dirtier drug with more S/Es but more efficacy

4) nexavar/sorafenib (bid dosing)

- **TKI that inhibits VEGFR-2, PDGFR, c-Kit, Flt3, and Raf kinase**
- increased progression-free survival in cytokine-refractory patients (6 vs 3 months)
- overall response rate only 2% but 70% showed a regression of tumour size (Escudier et al '05)

5) axitinib (AG-013736)

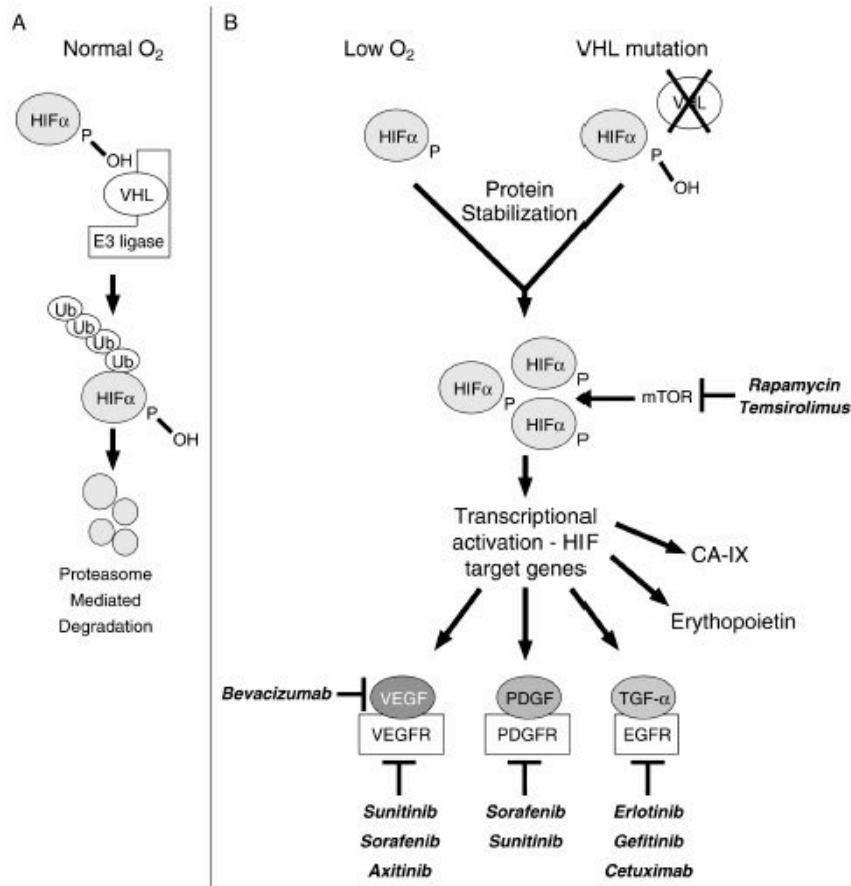
- **TKI that inhibits VEGFR-2, PDGFR, c-Kit, and Flt3**

6) temsirolimus (iv administration)

- **inhibits mTOR** and HIF/VEGF \ **also 1st line therapy for**
- improved survival over IL-2 / **high-risk metastatic RCC**

7) everolimus

- up and coming **TKI**



What are the common side effects of the targeted therapies?

- bevacizumab
 - HTN
 - proteinuria
 - epistaxis
- sunitinib/sutent
 - **pancytopenia (neutropenia most common side effect overall - ~40%)**
 - fatigue
 - **diarrhea (worse)**
 - GI upset
 - **HTN (worse)**
 - hand-foot desquamation syndrome
 - stomatitis
 - **decreased LVEF (5-10%)**
 - altered taste
 - dyspnea
- sorafenib/nexavar
 - **diarrhea (most common)**
 - fatigue
 - **hand-foot desquamation (worse)**
 - alopecia
 - GI upset
 - pruritus
 - **HTN**
 - sensory neuropathy
 - cough
 - dyspnea
- temsirolimus
 - **asthenia (most common)**
 - fever, chills
 - anorexia
 - GI upset
 - **dyspnea (worse)**
 - diarrhea
 - neutropenia/leukopenia

What is the role of cytokine combination therapy?

→ **increase in response rate when IL-2 & IFN α are combined } no overall survival benefit**

What is the role of adoptive immunotherapy?

→ no significant difference compared to cytokine therapy alone

→ addition of any ex vivo-expanded cell population to IL-2 is investigational only

What is the role vaccines?

→ currently investigational (eg incomplete Freund's adjuvant, BCG)

→ **autologous tumour cells, autologous tumour cells fused w/ allogeneic dendritic cells, autologous dendritic cell, heat shock protein**

Multimodal Therapy

What T cell abnormalities have been found in patients with advanced RCC?

- 1) altered signal transduction pathways
 - 2) abnormal activity of DNA-binding proteins
 - 3) poor proliferative responses
 - 4) increased T cell apoptosis
- may normalize after resection of primary
→ cytoreductive Nx with adjuvant cytokine Rx in setting of synchronous mets has been shown to be beneficial (Flanigan et al '01, Mickisch et al '01)

What is the role of adjuvant Nx after systemic therapy?

→ **unclear**

- allows selection of patients who have biologically more responsive tumours
- may be good in setting of solitary kidney with metastatic RCC } may do Partial Nx if there is response from systemic Rx
- most recommend Nx before systemic Rx ... but then some won't be able to get systemic Rx because of M&M from surgery } up to 30%

What are the prognostic factors associated with Cytoreductive Nx + metastectomy?

- solitary lung met } Piltz et al demonstrated median survival of 43months
- complete surgical resection
- mets <4cm
- tumour-free regional LNs

What is the role of salvage metastectomy?

- can be used in patients with residual or recurrent mets after an incomplete response to Rx
- decent results
 - cytoreductive Nx + IL-2 followed by resection of residual mets
 - 21month disease free survival (Kim and Louie '92)
 - immunotherapy followed by cytoreductive Nx + resection of mets
 - 3yr cancer-specific survival was 81.5% (Krishnamurthi et al '98)

OTHER MALIGNANT RENAL TUMOURS

Sarcomas of the Kidney

How common is renal sarcoma?

- 1-2% of all malignant renal tumours
- peak incidence in 40s
- less common but more lethal than sarcoma of any other GU site (prostate, bladder, paratesticular)
- sometimes difficult to differentiate from sarcomatoid variant of RCC

How do renal sarcomas present?

- flank mass
- flank/abdo pain
- hematuria
- apparent origin from capsule or perinephric region
- rapid growth to large size in absence of lymphadenopathy
- presence of fat or bone suggestive of liposarcoma or osteosarcoma
- **hypovascular pattern on angiography** → except hypervascular hemangiopericytoma

What are the common histologic subtypes of renal sarcoma?

- **leiomyosarcoma is MOST COMMON** } 50-60% → female predominance
 - } from smooth muscle cell of capsule or other perinephric structure
 - } tends to displace rather than invade parenchyma
 - } rapid growth, frequent mets, high local & systemic recurrence rates
- liposarcoma second most common } often confused with AML (fat-rich)
 - } grows to extremely large size
 - } respond to RADs + cisplatin-based chemo in adjuvant setting
- osteogenic sarcoma } rare, rock hard with extensive calcification
- rhabdomyosarcoma, fibrosarcoma, carcinosarcoma, MFH, synovial sarcoma, angiosarcoma, malignant hemangiopericytoma are all RARE

*****retroperitoneal sarcomas is reverse } liposarcoma most common, leiomyosarcoma 2nd*****

What are the common sites for mets of renal sarcoma?

- **lung is MOST COMMON**
- LNs
- liver

What are the prognostic factors for renal sarcoma?

- 1) **margin status } initial resection is key**
- 2) tumour grade

What are management options for renal sarcoma?

- derived from mesenchymal components that are free of many natural barriers to dissemination
- typically surrounded by pseudocapsule that is readily identifiable but can't be used for surgical dissection because it is often infiltrated with cancer cells
- high-grade sarcomas metastasize often } usually lungs
 - } poor prognosis (death in months)
- low-grade sarcomas tend to have an indolent course
- **surgical resection is MAINSTAY**
 - **radical Nx with en bloc resection } wide margins**
- CHEMO (ifosfamide, doxycycline) and RADs NOT great for renal sarcomas, even though they have been shown to be beneficial for sarcomas of the extremity

Renal Lymphoma and Leukemia

How common are renal lymphomas or leukemias?

- secondary disease found at autopsy in ~30%
- uncommonly seen clinically because they are often silent and often occur only late in disease
- **more common with non-Hodgkin's (NHL)** than HL
- renal leukemia more common in kids and more commonly lymphocytic (not myelogenous)
- **primary renal lymphoma is very rare (few cases)**
- more likely to be lymphoma than RCC if patient has history of immunosuppression, AIDS, autoimmune diseases, graft-vs-host disease, hx of radiation, previous lymphoma
- **90% hematogenous spread, ~10% direct extension, primary renal lymphoma rare**

How do renal lymphoma & renal leukemia present?

- usually silent and late manifestation of disease
- can have hematuria, flank pain, or ESRD
- B symptoms of lymphoma (wt loss, fevers, fatigue) are more common

What are the radiographic findings associated with renal lymphoma?

- **multiple renal masses (45%)**
- solitary renal mass (15%)
- renal invasion from enlarged retroperitoneal LNs (25%)
- diffuse renal involvement (10%)
- predominantly perinephric involvement (5%)
- hypovascular pattern on angiography
- concomitant splenomegaly, massive RPLNs, or lymphadenopathy in other regions of body

What is the management of renal lymphoma or leukemia?

- if suspected, arrange a **percutaneous Bx**
- if exploratory surgery is required, do intra-op Bx with frozen-section
- kidney spared if lymphoma or leukemia } systemic Rx
- Nx not usually indicated } except for severe uncontrollable hemorrhage or rare case of 1° lymphoma (Nx + CHEMO)

Metastatic Tumours

How common are metastatic renal tumours?

- **most common malignant tumour of kidney** } 12% of pts dying of Ca have renal mets on autopsy
- 1) **Lung } MOST COMMON**
- 2) **Breast**
- 3) **GI cancers**
- 4) malignant **Melanoma**
- 5) hematologic malignancies
- usually multifocal } lung, breast, and colon mets have been found to be large and solitary
 - } if long period of time since last tumour, likely RCC

How do metastatic renal tumours present?

- usually silent
- can cause hematuria and flank pain
- moderate enhancement on CT (5-30 HU)
- usually hypovascular pattern on angiography

What is the management of metastatic renal tumours?

- arrange percutaneous Bx if suspected
- systemic therapy usually initiated
- Nx not usually indicated } except for severe uncontrollable hemorrhage

Other Malignant Tumours of the Kidney

What other malignant tumours of the kidney are important?

- 1) renal carcinoid (<40 cases)
 - from neuroendocrine cells (not normally present in kidney)
 - **increased incidence in horseshoe kidneys**
 - **+ve urine or plasma serotonin** or its metabolites can be diagnostic
 - most asymptomatic } minority have carcinoid syndrome (flushing, wheezing, diarrhea)
 - usually small and nonaggressive

Rx → Nx is mainstay of treatment
→ consider C-scope and G-scope to assess for multifocal disease
- 2) adult Wilms' tumour
 - **most common renal malignancy in kids** but 3% of Wilms' tumours are seen in adults
 - anaplastic histology is unfavorable
 - heterogeneous intrarenal mass with relative hypovascularity
 - worse prognosis than pediatric Wilms' tumour

Rx → multimodal therapy recommended (same as kids)
→ Nx + CHEMO + RADs (high-grade)
- 3) primitive neuroectodermal tumour (PNET)
 - **related to the Ewing's sarcoma family of tumours seen in kids**
 - from primitive neural crest cells
 - usually a heterogeneous ill-defined mass with areas of necrosis
 - **usually minimal enhancement with contrast**
 - **renal PNET more aggressive than PNET in other sites**
 - early mets to LNs, lung, liver, and bone
 - high local recurrence
 - poor prognosis } 5yr disease-free survival is 50%

Rx → multimodal therapy
→ Nx + CHEMO + RADs
- 4) small cell carcinoma (30 cases)
 - must be differentiated on pathology from Wilms', PNET, lymphoma, and mets from lung small cell carcinoma
 - **characteristic +ve staining for neuron-specific enolase, chromogranin, synaptophysin**
 - usually locally advanced or metastatic at presentation

Rx → multimodal therapy
→ Nx + cisplatin-based chemo

NATURAL HISTORY

What chromosomal abnormalities are associated with upper tract TCC?

→ similar to that of bladder TCC

- p53 (chromosome 17) } **high grade disease**
- retinoblastoma gene (chromosome 13)
- proteins p18 and p16 (chromosome 9) } **low grade disease**

What is the distribution of upper tract TCC?

- 60% renal pelvis
- 35% ureter } 70% distal, 25% midureter, 5% proximal ureter
- 5% both renal pelvis and ureter
- **bilateral TCC (synchronous or metachronous) occurs in 1-6% of sporadic cases**

How common is bladder cancer in patients with upper tract TCC?

- **50-75% within 5yrs**

How common is upper tract TCC in patients with known bladder cancer?

- **incidence is 2-4%** } mean time to recurrence is 70 months
- higher in patients with CIS
- higher in patients that get a cystectomy for BCG-refractory CIS
- recurrence is usually superficial (Ta, T1, Tis) } debatable
- recurrence is usually in **distal ureter (~50%)**

What are the RFs for developing upper tract TCC in patients with bladder cancer?

- higher stage
- higher grade (eg 30% with BCG-treated CIS)
- multifocal bladder tumours
- presence of VUR
- recurrent CIS after BCG
- multifocal CIS at the time of cystectomy
- bladder cancers close to UO

What is the prognosis of upper tract TCC?

- often associated with poor prognosis } thin muscle layer of renal pelvis & ureter
- **~40% present with high grade, muscle invasive TCC** } cf ~25% in bladder TCC
- **~20% present with mets** } cf ~10% in bladder TCC
- prognosis is strongly related to stage } not as much grade

What is the route of dissemination of upper tract TCC?

- direct invasion into renal parenchyma or surrounding structures
- lymphatic invasion
- vascular invasion
- epithelial spread by seeding or direct extension

What are the predictors of developing metastatic upper tract TCC?

- stage
- grade
- renal parenchymal invasion } **most significant predictor of mets (95%)**
- vascular invasion } 80%
- lymphatic invasion } 75%

What are the 2 different theories on the etiology of upper tract TCC?

- 1) monoclonal theory } multiple tumours come from single abnormal cell that populates tract
→ majority of evidence favours this theory (particularly invasive TCC)
- 2) field theory } carcinogens bathe urothelium and multiple non-related tumours develop

What is the lymphatic drainage of the upper tract?

- renal pelvis, proximal ureter, and midureter } para-aortic and paracaval (depends on location)
- midureter and distal ureter } ipsilateral common iliac and pelvic

What are the most common sites of hematogenous spread of upper tract TCC?

- liver
- lung
- bone

PATHOLOGY

What are the layers of the upper urinary tract?

- urothelium starts at calyces and is continuous down to distal ureter into bladder
- calyces & renal pelvis } fibrous connective tissue (with fat cells) lies under 2 layers of smooth muscle
which are lined by transitional epithelium
} muscle layers originate in minor calyces and are in spiral, helical configuration
- ureter } 2 continuous smooth muscle layers lie beneath transitional epithelium in upper ureter
→ inner longitudinal
→ middle circular
} 3rd outer longitudinal smooth muscle layer present in distal ureter
} beneath outer smooth muscle lies serosa (loose connective tissue with vessels & lymphatics)

What is the significance of urothelial metaplasia and dysplasia?

- suggested that upper tract TCC progresses from hyperplasia to dysplasia to CIS
- severe dysplasia associated with greater risk for tumour recurrence in distal ureter & worse prognosis

What is the significance of upper tract inverted papillomas?

- itself benign but has been associated with upper tract TCCs } ~20%
- **monitoring recommended for at least 2yrs after initial Dx** of upper tract inverted papilloma

What are the most common upper tract tumours?

- 1) malignant
 - TCC (90%)
 - squamous cell carcinomas (~5%) } assoc'd w/ chronic inflammation, infection, analgesic abuse, cyclophosphamide
} 6x more common in renal pelvis than ureter
} usually high grade & more likely to be invasive at presentation
 - adenocarcinomas (<1%) } associated w/ long term obstruction, inflammation, stones
} usually present at advanced stage and have poor prognosis
 - sarcomas (rare) } includes leiomyosarcomas, plasmacytomas, angiosarcomas, etc
- 2) benign
 - fibroepithelial polyps } on a long stalk ("flaps in the breeze")
 - neurofibromas

PROGNOSTIC FACTORS

What are the prognostic factors associated with upper tract TCC?

- 1) stage } **the MOST IMPORTANT PREDICTOR of survival**
 - } T2 disease is seen early due to thinness of muscle layer
 - } big decrease in survival seen with T3 disease (penetration into perirenal or periureteral fat)
- 2) grade } less predictive of survival (predicts T stage though)
 - } high grade more likely to invade and more likely to be associated with CIS
 - ~80% of low grade is noninvasive, ~60% of high grade is invasive
- 3) associated CIS } predictive of lower survival
 - } more likely to have future invasive disease
 - } 30% of pts w/ bladder CIS treated w/ BCG develop CIS in distal ureter
- 4) LVI } independent prognostic factor for decreased survival
- 5) tumour aneuploidy } correlates with decreased overall survival
- 6) location } **CONTROVERSIAL**
 - } some say renal pelvic tumours have better prognosis (renal parenchyma serves as natural barrier) and ureteric tumours worse prognosis

What other factors are predictive of the diagnosis of upper tract TCC +/- prognosis?

- 1) molecular markers } **p53 +ve** associated with presence of upper tract TCC
 - } **telomerase activity** present in urine of >95% of upper tract TCC pts
 - } **urinary NMP22 elevated** in patients with upper tract TCC
 - } **decreased p27** (cyclin kinase inhibitor) assoc'd w/ worse survival
- 2) genetics } loss of heterozygosity at **chromosome 9p21** associated with upper tract TCC

DIAGNOSIS

How do upper tract TCCs usually present?

- **most common symptom is hematuria** (gross or micro) } found in >60%
- **flank pain** is 2nd most common symptom } ~30% of patients (from obstruction)
 - } usually dull and not acute (unless from clot)
 - } doesn't correlate with stage or prognosis
- ~15% are **asymptomatic** on presentation (incidentaloma)
- a filling defect is the most common finding on imaging (50-75%)
 - associated hydro linked with invasive disease

What imaging studies are used to diagnose upper tract TCC?

- CT urograms are replacing IVPs } may miss small filling defects (<5mm) between cuts
 - } high sensitivity (almost 100%) and high NPV (100%)
 - } provides more information on staging
- retrograde pyelogram } often performed to confirm and characterize filling defect
- U/S } not ideal study other than to see obstruction or large "filling defects"
- renal scan } used to determine function of contralateral "normal" kidney

What is the DDX of an upper tract filling defect?

- | | |
|--|---|
| <ul style="list-style-type: none"> - benign <ul style="list-style-type: none"> - blood clot - stones - sloughed papilla - fungus ball - fibroepithelial polyp - overlying bowel gas - external compression | <ul style="list-style-type: none"> - malignant <ul style="list-style-type: none"> - TCC - SCC - adenocarcinoma - sarcoma |
|--|---|

What are the advantages & disadvantages of ureteroscopy for upper tract TCC?

ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none">- improves diagnostic accuracy when combined with CT urogram or IVP (75% to 85-90%)- benefit of direct visualization of tumour- benefit of getting Bx or brushings- grade of Bx correlates well with final pathology grade	<ul style="list-style-type: none">- correlation of small Bx specimen to stage of tumour is poor- rare case reports of tumour seeding and dissemination (extravasation or pyelovenous/pyelolymphatic spread)- may be more likely to treat tumour endoscopically, thereby providing inadequate treatment
→ URETEROSCOPY IS NOT NECESSARY FOR ALL CASES	
→ SHOULD BE RESERVED FOR DIAGNOSTIC DILEMMAS OR WHERE RX MAY BE MODIFIED ON THE BASIS OF FINDINGS	

What are the historical signs on retrograde pyelography that makes Dx of TCC more likely?

- goblet sign } with stone, ureteral spasm results in non-goblet pattern
- Bergman's sign } ureteric catheter curls when it hits tumour but doesn't curl as much with stone

What is the role of antegrade endoscopy?

- may be required in some cases of upper tract tumours } Dx or treatment
- can use larger caliber scopes for visualization, biopsy or resection of tumour
- implantation into retroperitoneum and NT tract have been reported

What is the role of urinary cytology in upper tract TCC?

- specific but poor sensitivity } grade dependent
- ureteral washings more accurate than voiding cytology/bladder washings
- brush biopsy even more accurate
- exposure to **contrast dye may worsen cytologic abnormalities**

STAGING

What is the TNM staging system for upper tract TCC?

- T Stage
 - Ta – papillary noninvasive
 - Tis – CIS
 - T1 – invades subepithelial connective tissue (lamina propria)
 - T2 – invades into muscularis propria
 - T3 – invades into periureteral fat, perinephric fat, or into renal parenchyma
 - T4 – invades adjacent organ or through kidney into perinephric fat
- N Stage
 - N1 – mets to single LN (≤ 2 cm)
 - N2 – mets to single LN (2-5cm) or multiple LNs (all < 5 cm)
 - N3 – mets to LN > 5 cm
- M Stage
 - M1 – distant mets

What is the AJCC staging system of upper tract TCC?

- stage 1 } anything $< T2$ and No, Mo
- stage 2 } $T2$ and No, Mo
- stage 3 } $T3$ and No, Mo
- stage 4 } $T4$ or any T and N+, M+

*** UPPER TRACT TCC TENDS TO BE UNDERSTAGED ***

TREATMENT

Endoscopic Resection or Fulguration

What are the indications for endoscopic management of upper tract TCC?

- tumour in solitary kidney
- synchronous bilateral tumours
- renal dysfunction
- significant co-morbidities that preclude major surgery
- ? select patients with small, low-grade, non-invasive lesions (normal contralateral kidney)

What is the survival data for endoscopic management of upper tract TCC?

- low-grade, low-stage lesions } excellent
 - } recurrence likely and can have progression even with close f/u
 - high-grade } even if low stage, limited by the field effect and commonly associated CIS
 - T1 or T2 disease } limited by adequacy of determining depth of tumour
 - } can't resect too deep due to risk of bleeding, perforation
- **recurrence rates ~30-35% } higher with high grade (50%)**
- risk of bladder TCC is ~40-50%
- **grade and stage are most important predictors of recurrence**
- should be reserved for LOW GRADE, LOW STAGE tumours

What are the indications for antegrade/percutaneous endoscopic management of upper tract TCC?

- large tumour volume
- renal pelvis or calyceal location
- high grade tumour not amenable to nephroureterectomy
 - if high grade, nephroureterectomy recommended whenever possible (better outcomes)

Segmental Ureterectomy

What are the indications for segmental ureterectomy for upper tract TCC?

- 1) invasive tumours where nephron-sparing surgery is necessary (eg solitary kidney)
- 2) high grade tumours where nephron-sparing surgery is necessary (eg bilateral tumours)
- 3) low grade, non-invasive tumour in distal ureter
- 4) low grade, non-invasive tumours of proximal or midureter too large for endoscopic mgt
- 5) low grade, T2 tumours of proximal or midureter

What is the survival data for segmental ureterectomy for upper tract TCC?

- **outcomes largely depends on tumour grade and stage**
- 55-80% for low grade BUT ~15% for high grade
 - 5yr survival for Ta tumours is similar to endoscopic mgt } ~80%
 - 5yr survival for T1 tumours is ~65%
 - 5yr survival for T2 tumours is ~50%
 - 5yr survival for T3 tumours is ~20%
- **risk of ipsilateral recurrence is 45-50%**
- **inspection of ureter proximal to tumour is essential } either pre-op or intra-op**

Nephroureterectomy

What are the indications for nephroureterectomy for upper tract TCC?

→ **GOLD STANDARD**

- large, high-grade, invasive tumours
- large, multifocal, non-invasive tumours of renal pelvis or proximal ureter
- large, rapidly recurring, non-invasive tumours of renal pelvis or proximal ureter

What are the indications to perform an ipsilateral adrenalectomy at the time of nephroureterectomy?

- upper collecting system tumour
- imaging suspicious for adrenal involvement by direct extension
- large, advanced tumours } adrenal is common site of mets
- palpably abnormal adrenal intra-op

What are the principles of a nephroureterectomy?

- don't compromise urinary tract } tumour spillage
- entire ureter must be resected, including intramural ureter and UO
 - **risk of recurrence in ureteral stump is 35-75%**
- lymphadenectomy only if suspicious LNs on pre-op imaging } **CONTROVERSIAL TOPIC**
 - } little therapeutic value as most patients with N+ disease have developed early M+ disease

List options for dealing with the distal ureter when performing a nephroureterectomy.

→ **must remove entire distal ureter including the intramural portion and UO**

→ **risk of tumour recurrence in distal stump is 30-75%**

- 1) traditional open distal ureterectomy
 - transvesical } anterior cystotomy aids in complete resection of distal ureter and UO
 - } include 1cm bladder cuff
 - extravesical } avoids need for cystotomy
 - } must be careful to ensure complete dissection of intramural ureter and UO as well as avoiding injury to contralateral UO
 - } take bladder cuff
- 2) transurethral resection of UO (aka Pluck technique)
 - **reserved for proximal, low-grade tumours**
 - UO and intramural ureter aggressively resected out to extravesical space
 - avoids need for second incision } not so big a deal for lap (extraction site needed)
- 3) intussusception (stripping) technique
 - Nx carried out as per usual but with ureteral catheter in place
 - ureter transected as distal as possible
 - distal end of ureter is intussuscepted using secured ureteral catheter and specimen is resected with bladder cuff
 - **high rate of disruption of ureter needing 2nd incision (20%)**
- 4) transvesical lap ligation and detachment
 - lap instruments placed via suprapubic transvesical trocars
 - stent placed then ureter tented up and loop ligature used to create closed system
 - Collins knife used to dissect out ureter to the extravesical space
 - **technically difficult**
- 5) total laparoscopic
 - Bugbee used to cauterize intramural ureter and UO completely
 - antegrade traction is placed on ureter during laparoscopic portion of operation
 - endovascular stapler used as distally as possible
 - confirmation of removal of entire ureter with cystoscopy

What is the survival data for nephroureterectomy for upper tract TCC?

- overall 5yr survival is ~85%
- **outcomes strongly correlate with tumour stage & grade**

What is the role of laparoscopic nephroureterectomy?

- same indications as for open
- no significant difference b/w lap, lap + open, or open } lap does have better morbidity profile
- few case reports of port site seeding } all had compromised principles of surgical oncology

What are the indications for adjuvant chemotherapy?

- ≥T3 disease
- N+ disease
- cisplatin based
- precise role of adjuvant chemo in setting of locally advanced disease not well defined
- if large mass or bulky LNs, consider NEO-adjuvant chemo

Partial Nephrectomy

What are the indications for partial nephrectomy for upper tract TCC?

- tumour in solitary kidney
- synchronous bilateral tumours
- renal dysfunction
- predisposition to form multiple recurrences (eg Balkan nephropathy, analgesic-related)
- **largely replaced by endoscopic management**
- for renal pelvic tumours, open approach preferable over lap because of high likelihood of tumour spillage and implantation

What is the survival data for partial nephrectomy for upper tract TCC?

- **10-60% risk of ipsilateral recurrence } depends on grade**
- 2yr survival for high grade disease is <50%
- NU likely better for high grade, muscle invasive, organ-confined TCC even if on dialysis after
 - depends on patient age } elderly may wish to live out their yrs off dialysis
- **risk of recurrence depends on grade and stage**

Topical Immunotherapy and Chemotherapy

What is the role of topical immunotherapy or chemotherapy?

- to reduce recurrence
- to definitively treat upper tract TCCs
- successful use of BCG, mitomycin C, doxorubicin, and thiotepa described

What are the methods of delivering upper tract topical therapy?

- antegrade instillation via NT
- retrograde reflux from bladder via ureteric stent
- instillation via retrograde catheter

What is the survival data for upper tract topical therapy?

- recurrence rates 30-50%
- **most studies haven't shown statistically significant improvement in overall survival**

Chemotherapy for advanced disease

What is the role for chemotherapy in advanced upper tract TCC?

→ **upper tract TCC is relatively chemosensitive BUT outcomes are poor**

- single agent therapy has response rates only in the 25-35% range
eg cisplatin, MTX, cyclophosphamide, gemcitabine
- **combination therapies are often used } MVAC, GC**
- relative low prevalence of upper tract TCC has limited the clinical trials

FOLLOW-UP

What is the recommended surveillance schedule after treatment for upper tract TCC?

- 1) physical exam + urine cytology + cystoscopy
 - q3months for 1st yr, then q6months for years 2-3, then yearly thereafter
 - cytology has greater utility for high-grade TCC
- 2) IVP or retrograde or CT urogram
 - yearly
- 3) ipsilateral ureteroscopy (after nephron-sparing surgery) } imaging alone can miss up to 75% of early recurrences
 - q6months for first 3yrs
 - yearly thereafter
- 4) metastatic evaluation (for high grade or invasive disease)
 - CXR, CBC, lytes, creatinine, LFTs } q3months for 1st yr, q6months for years 2-3, yearly for years 4-5
 - CT or MRI } q6months for first 2yrs then yearly until year 5
 - bone scan } only if elevated ALP or symptoms

Chapter #49 – Management of Upper Tract TCC

What is the 5yr disease-specific survival data for upper tract TCC?

- frequency is increasing
- overall survival is 75%
- CIS } ~95%
- localized } 40-90%
- T3, T4 } 5-50%
 - worse if T3 of ureter than renal pelvis
- N+ } 0-5%
- M+ } 0-1%
- high grade } 0-33%
- low grade } 40-87%

What are the tumour characteristics of upper tract TCC on presentation?

- 1) renal pelvis
 - 85% of renal pelvis tumours are papillary
 - similar to bladder Ca
 - however, 50% of these papillary lesions are T1 or T2
 - 15% of renal pelvis tumours are sessile
 - 80% of these are T1 or T2
 - **SO OVERALL, 50-60% OF RENAL PELVIS TUMOURS ARE INVASIVE**
- 2) ureter
 - 55-75% of ureteral tumours are low grade and low stage
 - invasive disease still more common than bladder

What is the distribution of upper tract TCCs?

- 65% renal pelvis
- 30% ureter } 70% distal, 25% midureter, 5% proximal ureter
- 5% both renal pelvis and ureter

How common is ipsilateral recurrence of upper tract TCC after conservative treatment?

- occur in a proximal to distal direction
- 35-55% of cases
- rare to see recurrence proximal to original tumour

How common is upper tract TCC after bladder TCC?

- 2-4%
- mean time to occurrence is 70months
- 15-50% of all upper tract TCC cases occur in patients with a hx of bladder TCC
- upper tract TCC occurs in 3-9% of patients post-cystectomy for bladder TCC
 - 25% have CIS in distal ureter if cystectomy done for bladder CIS
- upper tract TCC seen in ~30% of patients successfully treated with BCG for bladder CIS

How common is bladder TCC after upper tract TCC?

- 20-75%
- occurs much sooner than does upper tract TCC after bladder TCC (20months vs 70months)

What are the specific characteristics of upper tract TCC associated with Balkan nephropathy or analgesic abuse?

- high tendency to be **multiple & bilateral but usually low-grade**
- often associated with renal insufficiency
- degree of renal papillae scarring seen in phenacetin abuse correlates w/ risk of high grade tumours & progression
- calcification of renal papillae after analgesic abuse is associated with SCC of renal pelvis
- important to offer conservative treatment when possible

What are the prognostic factors associated with upper tract TCC?

- **STAGE is the single most important factor**
- grade } strongly correlates with stage
- location } renal pelvic tumours tend to do better
- associated CIS
- LVI

What are the common sites of mets for upper tract TCC?

- lung - bones
- liver - regional LNs

What are the staging investigations prior to surgical management of upper tract TCC?

- CXR
- triphasic CT abdo/pelvis
- CBC, lytes, creatinine, LFTs, Ca profile
- bone scan when indicated

OPEN NSS FOR RENAL PELVIS TUMOURS: PYELOTOMY with TUMOUR ABLATION AND PARTIAL NEPHRECTOMY

What are the indications for open NSS for renal pelvic TCC?

→ **largely replaced by endoscopic management**

- tumour in solitary kidney
- synchronous bilateral tumours
- renal dysfunction
- predisposition to form multiple recurrences (eg Balkan nephropathy)
- for renal pelvic tumours, open approach preferable over lap because of high likelihood of tumour spillage & implantation

What is the survival data for partial nephrectomy for upper tract TCC?

- 10-60% risk of ipsilateral recurrence
- 2yr survival for high grade disease is <50%
- NU likely better for high grade, muscle invasive, organ-confined TCC even if on dialysis after
 - depends on patient age } ie elderly may wish to live out their yrs off dialysis
- **risk of recurrence depends on grade and stage**

Describe open NSS for renal pelvis tumours?

- approach similar to partial nephrectomy for RCC
- place sponges around kidney to isolate kidney and prevent seeding if spillage occurs
- pyelotomy with tumour ablation } open pelvis after completely dissecting renal pelvic fat
 - } remove tumour and fulgurate base and edges
 - } close renal pelvis
 - } no stent unless difficult to close collecting system
- partial Nx } similar to PNX for RCC
 - } clamp off involved segment of collecting system before removal of tumour-bearing portion of kidney

OPEN RADICAL NEPHROURETERECTOMY

What are the indications for nephroureterectomy for upper tract TCC?

→ GOLD STANDARD

- large, high-grade, invasive tumours of renal pelvis or proximal ureter
- large, multifocal, non-invasive tumours of renal pelvis or proximal ureter
- large, rapidly recurring, non-invasive tumours of renal pelvis or proximal ureter

What are the different approaches to an open radical nephroureterectomy?

- extrapleural, extraperitoneal, thoracoabdominal incision } big cut but best exposure
- intraperitoneal midline incision } limited exposure, especially for left side
- upper anterior subcostal incision + Gibson incision } instead of Gibson can use Pfannenstiel or lower midline incision
} anterior approach difficult in obese pts

What are the options for the distal ureterectomy?

→ **must remove entire distal ureter including the intramural portion and UO**

→ **risk of tumour recurrence in distal stump is 30-75%**

- 1) traditional open distal ureterectomy
 - transvesical } anterior cystotomy aids in complete resection of distal ureter and UO
} include 1cm bladder cuff
 - extravesical } avoids need for cystotomy
} must be careful to ensure complete dissection of intramural ureter and UO as well as avoiding injury to contralateral UO
} take bladder cuff
- 2) transurethral resection of UO
 - aka Pluck technique
 - **reserved for proximal, low-grade tumours**
 - UO and intramural ureter aggressively resected out to extravesical space
 - avoids need for second incision } not so big a deal for lap (extraction site needed)
- 3) intussusception (stripping) technique
 - nephrectomy carried out as per usual but with ureteral catheter in place
 - ureter transected as distal as possible
 - distal end of ureter is intussuscepted using secured ureteral catheter and specimen is resected with bladder cuff
 - **high rate of disruption of ureter needing 2nd incision (20%)**
- 4) transvesical lap ligation and detachment
 - lap instruments placed via suprapubic transvesical trocars
 - ureteric stent placed
 - ureters tented up and loop ligature used to create a closed system
 - Collins knife used to dissect out ureter to the extravesical space
 - **technically difficult**
- 5) total laparoscopic
 - Bugbee used to cauterize intramural ureter and UO completely
 - antegrade traction is placed on ureter during laparoscopic portion of operation
 - endovascular stapler used as distally as possible
 - confirmation of removal of entire ureter with cystoscopy

What is the role of lymphadenectomy at the time of nephroureterectomy for upper tract TCC

- **regional lymphadenectomy is included with radical nephroureterectomy**
- renal pelvis and proximal ureteric TCC } **renal hilar LNs, para-caval or para-aortic LNs**
- not done in patients with severe atherosclerosis of the aorta or grossly positive/fixed nodes

What are the pros & cons of lymphadenectomy at the time of nephroureterectomy for upper tract TCC?

PROS

- adds little time or morbidity to surgery
- gives prognostic information
- might have therapeutic value

CONS

- **no studies have shown a therapeutic benefit**

LAPAROSCOPIC RADICAL NEPHROURETERECTOMY

What are the indications for lap nephroureterectomy for upper tract TCC?

- same as for open nephroureterectomy

What are the different approaches to lap radical nephroureterectomy?

- transperitoneal
- retroperitoneal
- hand-assisted

➔ **incision for specimen removal should be used to also aid in dissection out distal ureter**

What is the survival data for laparoscopic nephroureterectomy?

➔ **similar survival data as open NU but with decreased morbidity**

- local recurrence rate ~2%
- bladder recurrence rate ~25%
- rate of distant mets ~10%
- +ve margins in ~5%

OPEN SEGMENTAL URETERECTOMY

What are the indications for segmental ureterectomy for upper tract TCC?

- 1) invasive tumours where nephron-sparing surgery is necessary
- 2) high grade tumours where nephron-sparing surgery is necessary
- 3) low grade, non-invasive tumour in distal ureter
- 4) low grade, non-invasive tumours of proximal or midureter too large for endoscopic mgt
- 5) low grade, T2 tumours of proximal or midureter

What are some of the principles of the segmental ureterectomy for upper tract TCC?

- ligate ureter 1-2cm proximal and distal to tumour
- frozen-section sent to confirm tumour and to assess ends of ureter
- regional lymphadenectomy
- spatulated, water-tight, tension free UU over a stent
- leave JP drain

What are the indications for complete distal ureterectomy?

- distal tumour that can't be removed endoscopically in patient needing nephron-sparing sx
- usually larger, high grade, invasive lesions

What are the options for ureteric reimplantation?

- direct ureteroneocystostomy } only if a short segment removed
- psoas hitch } 6-10cm
- Boari flap } 12-15cm
- renal descensus } 5-8cm

What are the arguments for a refluxing vs a non-refluxing reimplantation?

- controversial
- refluxing } facilitates f/u surveillance of upper tract with ureteroscopy and imaging studies
- non-refluxing } limits infections
- } limits seeding of upper tract with tumours from bladder

What are the indications for subtotal ureterectomy?

- multifocal, low grade, non-invasive tumours
- multifocal, high grade or invasive tumours where nephron-sparing surgery is necessary

What are the options after subtotal ureterectomy?

- complete ileal ureter
- ileal interposition } ileum narrowed over 14Fr catheter
- vermiform appendix interposition
- renal autotransplantation + pyelocystostomy } for total ureterectomy

What is the 5yr survival data after segmental ureterectomy?

→ highly dependent on stage and grade

- 55-80% for low grade BUT ~15% for high grade
- Ta, T1 } 60-80%
- T2 } ~50%
- T3 } ~20%
- T4, N+, M+ } ~0%

What is the risk of ipsilateral recurrence after conservative management of ureteral tumours?

- 33-55%
- usually occur distal to primary
- needs lifelong surveillance

ENDOSCOPIC TREATMENT

What are the indications for endoscopic management of upper tract TCC?

- solitary kidney
- bilateral disease
- renal dysfunction
- significant co-morbidities that preclude major surgery
- ? select patients with small, low-grade, non-invasive lesions (normal contralateral kidney)

What are the different approaches to endoscopic management of upper tract TCC?

- retrograde } for smaller ureteral or renal tumours
- antegrade } for large tumours of upper ureter or kidney
- } difficult to access via retrograde approach eg lower pole, ureteroenteric anast.
- should be reserved for **LOW GRADE ONLY**

What are the advantages of the retrograde & antegrade approaches?

- 1) retrograde
 - no compromise of the collecting system
 - avoids percutaneous tract (less morbidity)
- 2) antegrade
 - ability to use larger instruments and remove a large volume of tumour
 - better biopsy specimens } usually get better stage information

What are the advantages & disadvantages of flexible ureteroscopes?

→ usually reserved for upper or renal TCC } semirigid used for distal or midureter

→ ADVANTAGES

- less ureteric trauma
- can reach upper ureter and kidney

→ DISADVANTAGES

- small working channel } limited flow and small instruments
- difficult to access lower pole if acute angle
- difficult to access ureter if prior urinary diversion

What are the 3 general approaches for tumour ablation?

- 1) bulk excision with ablation of base } good for low grade lesions on thin stalk
 - 2) resection of tumour to base + Bx of base } good for large, broad-based tumours
 - 3) diagnostic Bx then ablation with cautery or laser
- if antegrade approach taken, leave NT so f/u nephroscopy can be performed 1-2weeks later

What are the characteristics of the Ho:YAG and Nd:YAG lasers used for fulguration?

- Ho:YAG } PREFERRED
 - minimal penetration (<0.5mm)
 - efficient ablation of tumour
 - precise cutting
 - setting 0.6-1.2joules/8-10 Hz
- Nd:YAG
 - deep penetration (5-6mm)
 - excellent hemostasis
 - tumour ablation by coagulative necrosis
 - setting 20-30watts

What are the complications of ureteroscopic management of upper tract TCC?

- perforation
- stricture
- inadequate Bx specimen

What are the potential complications of antegrade endoscopic management of upper tract TCC?

- bleeding
- perforation of collecting system
- secondary UPJO
- NT track seeding (rare)

What are the survival data for endoscopic management of upper tract TCC?

→ **depends highly on stage and grade**

- survival for non-invasive, low grade disease is 90-95%
- overall ureteral recurrence rate is ~30%
- overall renal pelvic recurrence rate is ~30%
- risk of bladder recurrence is ~45%

ISOLATED UPPER TRACT CYTOLOGIC ABNORMALITIES OR URINARY MARKERS

What is the management of isolated abnormal cytology (or other urinary marker) from the upper tract?

- normal IVP, retrograde, cystoscopy + normal bladder & urethral Bx + abnormal cytology from one side
- ureteroscopy
 - persistently abnormal cytology may indicate CIS
 - NU no longer recommended
- instillation of topical immunotherapy or chemotherapy may be an option } limited data
- close surveillance without overtreatment is essential

ADJUVANT THERAPY

What are the 2 major adjuvant therapies available after nephron-sparing treatment for upper tract TCC?

- 1) instillation of immunotherapy or chemotherapy } no statistical improvement in survival
- 2) brachytherapy of NT track

What are the options for instillation of immunotherapy or chemotherapy?

- antegrade instillation via NT
- retrograde instillation via ureteral catheter
- retrograde refluxing instillation via ureteral stent + bladder instillation

What are the contraindications to instillation of immunotherapy or chemotherapy into the upper tracts?

- active infection
- high pressure instillation

What are the options for adjuvant therapy following NU?

- 1) RADS
 - for T3-T4, N+ disease
 - may slightly decrease recurrence
 - NO BENEFIT FOR DISTANT RELAPSE
 - NO SURVIVAL BENEFIT
- 2) systemic chemo
 - no good studies on neoadjuvant or adjuvant chemo

FOLLOW-UP

What is the recommended surveillance schedule after treatment for upper tract TCC (CHART)?

- 1) physical exam + urine cytology + cystoscopy
 - q3months for 1st yr, then q6months for years 2-3, then yearly thereafter
 - cytology has greater utility for high-grade TCC
- 2) IVP or retrograde or CT urogram
 - yearly
- 3) ipsilateral ureteroscopy (after nephron-sparing surgery) } imaging alone can miss up to 75% of early recurrences
 - q6months for first 3yrs
 - yearly thereafter
- 4) metastatic evaluation (for high grade or invasive disease)
 - CXR, CBC, lytes, creatinine, LFTs } q3months for 1st yr, q6months for years 2-3, yearly for years 4-5
 - CT or MRI } q6months for first 2yrs then yearly until year 5
 - bone scan } only if elevated ALP or symptoms

TREATMENT OF METASTATIC DISEASE

What is the management of metastatic upper tract TCC?

→ **outcomes are poor**

→ systemic chemo regimes offered are the same as for bladder TCC

→ lesions are rare so there is limited data on response rates

- 1) MVAC (MTX, vinblastine, doxorubicin, cisplatin)
 - highest response rate
 - almost never see CR
 - high toxicity
 - **overall survival is 12-24months**
- 2) newer agents with similar response rates but better toxicity profile
 - cisplatin
 - gemcitabine
 - paclitaxel
 - ifosfamide

- undergoes compensatory hypertrophy
- **GFR maintained at ~75% of normal value**
- no increase in HTN or proteinuria w/ stable overall renal fxn & no change in life expectancy
 - recent data suggests that RCC Nx patients may differ from donor Nx patients
 - RCC Nx patients may be at slightly higher risk of future renal dysfunction

INTRA-OP RENAL ISCHEMIA

What are the indications for temporary renal artery occlusion?

- diminishes renal bleeding
- improves access by causing kidney to contract (reduced turgor)
- 1) partial Nx
- 2) renal vascular reconstruction
- 3) anastrophic nephrolithotomy
- 4) repair of traumatic renal injuries

What pathophysiologic processes contribute to renal injury from ischemia?

- persistent vasoconstriction } due to activation of tubuloglomerular feedback from enhanced delivery of solute to macula densa
 - leukocyte activation } results in further endothelial injury and contributes to production of local factors that promote vasoconstriction
 - changes in local vasoactive substances } ↑'d activity of AT₂, TXA₂, LTs, endothelin-1, etc
 } ↑'d basal tone and reactivity of arterioles to vasoconstrictive agents with decreased vasodilatory responses
 } inhibition of endothelial NO, a vasodilatory agent
 - reperfusion injury } infiltration of neutrophils & mononuclear cells results in tubular damage
 } reperfusion induced activation of coagulation pathways also lead to tissue injury
- outer medulla (PCT cells) is most at risk of ischemic injury**

How much warm ischemia is tolerated by the kidney?

- **30 minutes** } renal warm ischemia beyond 30 minutes results in significant, immediate fxn'l loss and late recovery of renal function is either incomplete or absent
- **PCT cells are the most sensitive to renal ischemia**
- glomeruli and blood vessels are generally spared

Name situations in which the kidney tolerates longer periods of warm ischemia?

- 1) **solitary kidney** more resistant to ischemic damage
- 2) presence of extensive **collateral vasculature** (ie renal arterial occlusive disease) associated with higher tolerance of temporary renal arterial occlusion
- 3) temporary **occlusion of renal artery alone** (renal vein open)
→ retrograde perfusion permitted
- 4) **continuous clamping**
→ intermittent clamping of the renal artery with short periods of recirculation results in more renal damage
→ possibly related to release & trapping of damaging vasoconstrictor agents w/in kidney
- 5) **avoidance of manual renal compression**
→ simple arterial occlusion better tolerated than manual renal compression

What are the different ways to reduce/prevent ischemic renal damage?

- generous pre-op and intra-op **hydration**
 - **prevention of hypoTN** during OR
 - **avoidance of unnecessary manipulation** or traction on renal artery
 - intra-op **mannitol** } most effective when given 5-15 mins before clamping
 - renal **hypothermia** } reduces metabolic activity of cortical cells
 - } optimal temp is 15C
 - } provides complete renal protection from arterial occlusion for up to 3hrs
 - } external surface cooling w/ slush-ice (10-15mins before starting renal incision)
- VS perfusion of kidney with intra-arterial cold solution

What are the beneficial effects of mannitol?

- osmotic diuresis } keeps tubules flushed free of casts
- free radical scavenger } prevents reperfusion injury
- prevents cell edema
- protects mitochondrial function
- ↑'s RBF/GFR
- ↓'s intra-renal vascular resistance

What is the role of pharmacologic agents to prevent post-ischemic renal failure?

- proposed agents include } dopamine
- } inosine
- } captopril
- } adenosine triphosphate-Mg

→ **no consistent renoprotective effect shown for any agent**

SURGICAL APPROACHES TO THE KIDNEY

What are the factors to consider when deciding on type of incision for renal surgery?

- type of operation to be performed
- underlying renal disease
- previous operations
- concurrent extrarenal disease that requires another operation to be done simultaneously
- need for bilateral renal operations
- body habitus

What are the main approaches to the kidney?

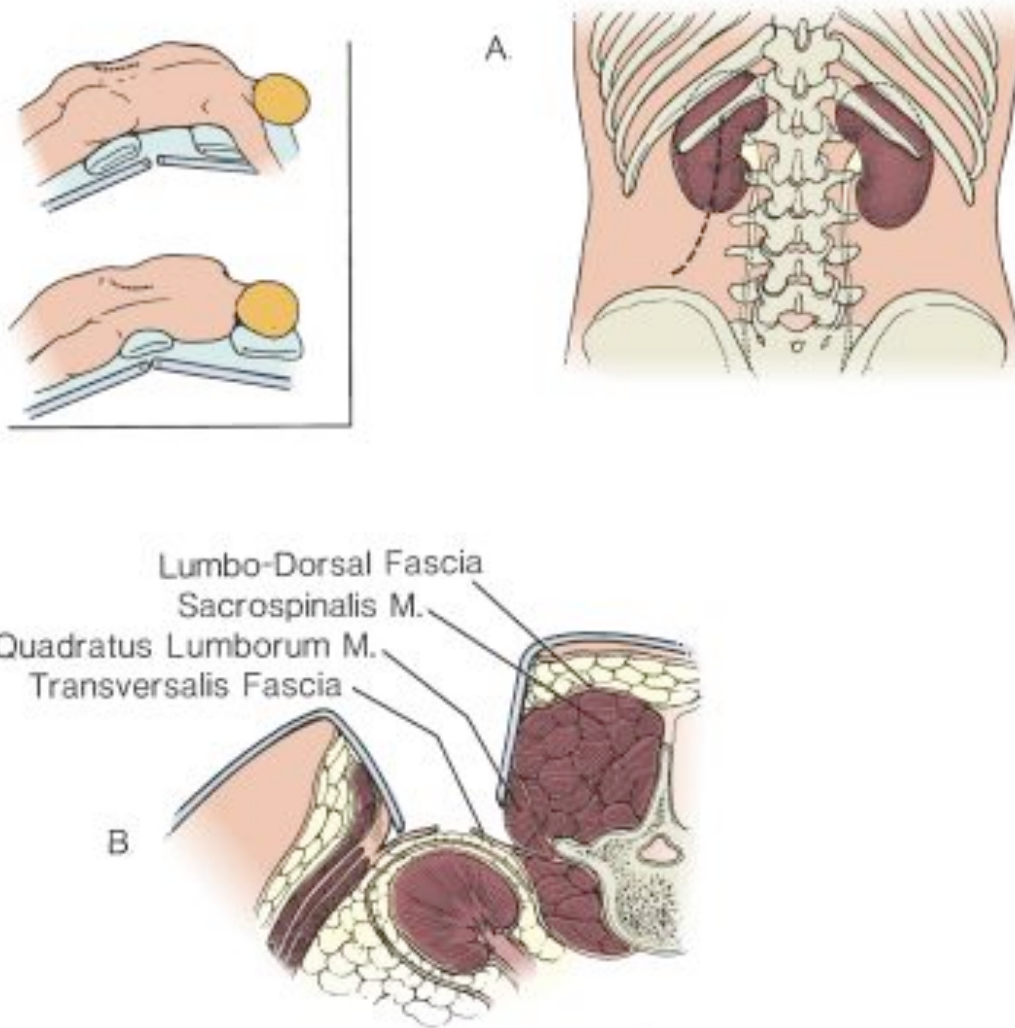
- flank (extraperitoneal and intraperitoneal)
- subcostal flank
- abdominal
- thoraco-abdominal
- dorsal lumbotomy

What are the advantages & disadvantages of the different approaches to the kidney?

	ADVANTAGES	DISADVANTAGES
flank incision	<ul style="list-style-type: none">- good for obese patients- minimal disturbance of peritoneum	<ul style="list-style-type: none">- suboptimal exposure of hilum- not good for scoliosis or severe cardiopulmonary disease
subcostal flank	<ul style="list-style-type: none">- less painful incision because avoids ribs- good access to lower pole- avoids pleura	<ul style="list-style-type: none">- access to hilum and renal pelvis difficult (in adults)- difficult to access upper pole
abdominal	<ul style="list-style-type: none">- excellent exposure to renal hilum- diversity of incisions to maximize exposure (vertical, subcostal, paramedian, chevron)	<ul style="list-style-type: none">- longer post-op ileus- possible development of intra-abdominal complications (eg adhesions, SBO)
thoraco-abdominal	<ul style="list-style-type: none">- good for large upper pole tumours (esp on right side)	<ul style="list-style-type: none">- takes longer- higher pulmonary morbidity and requires chest tube post-op
dorsal lumbotomy	<ul style="list-style-type: none">- good for removal of small kidneys, B/L Nx for ESRD, open renal biopsy, pyeloplasty, upper ureterolithotomy- fast and less painful (avoid muscle cuts)- good if previous flank or abdo surgery	<ul style="list-style-type: none">- limited access to kidney & hilum (poor access if complication eg major vessel injury)- not good for large kidneys

How is a dorsal lumbotomy incision made?

- patient placed in lateral decubitus position
 - prone if bilateral renal access needed
- vertical lumbar incision made along lateral margin of sacrospinalis muscle
 - starting at upper margin of 12th rib down to iliac crest, with gentle lateral curve
- incision carried through lumbodorsal fascia, just lateral to sacrospinalis and quadratus lumborum muscles, which are then retracted medially
- transversalis fascia incised to expose kidney within Gerota's fascia



SIMPLE NEPHRECTOMY

What are the indications for simple nephrectomy?

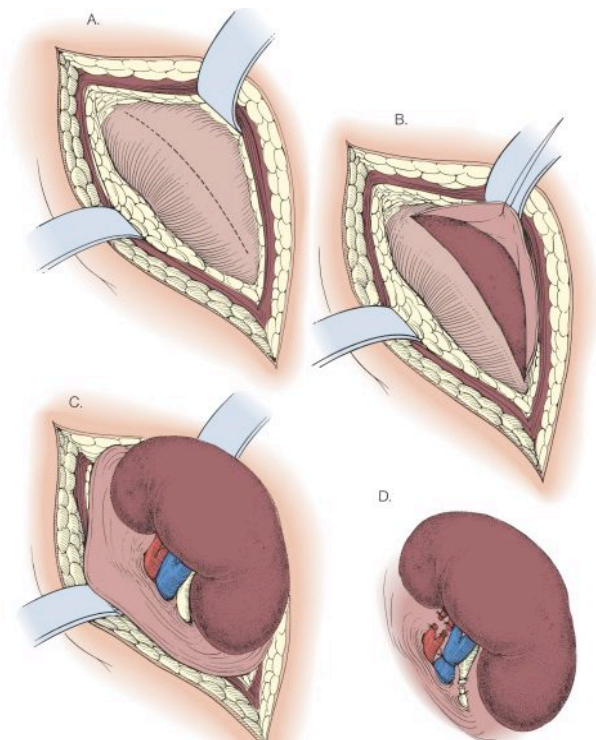
- 1) normal contralateral kidney and irreversibly damaged kidney due to:
 - symptomatic chronic pyelonephritis
 - obstruction
 - stones
 - severe traumatic injury
 - PCKD
- 2) renovascular HTN due to:
 - uncorrectable renal artery disease
 - severe unilateral parenchymal damage from nephrosclerosis, reflux, pyelonephritis, or congenital dysplasia
- 3) donor Nx

What is the best approach for a simple nephrectomy?

- extraperitoneal flank approach } chronically infected kidney
 - } obese patient
 - } hx of previous abdo surgery
- abdominal approach } those that can't tolerate flank position
 - } B/L nephrectomy for ESRD due to PCKD
 - } traumatic renal injury that requires early access to hilum
 - } hx of previous flank surgery

When is a subcapsular simple nephrectomy indicated?

- severe perirenal inflammation precludes safe dissection between kidney & surrounding structures
eg Tx nephrectomy
- open renal capsule along lateral surface of kidney and dissect between parenchyma & capsule down to level of hilar vessels



→ SUBCAPSULAR NEPHRECTOMY

RADICAL NEPHRECTOMY

What is the pre-op w/u prior to a Radical Nx?

- hx and P/E
- bloodwork } cbc, lytes, creatinine, LFTs, ALP, Ca, coags
- triphasic CT abdo/pelvis
- CXR } chest CT if abN or if symptoms
- bone scan } only if symptomatic or elevated ALP
- MRI or TEE } reserved for those with IVC thrombus
- coronary angiography } if tumour thrombus extends to atrium and patient will go on pump

What are the indications for Radical Nx?

- 1) localized RCC
- 2) metastatic RCC with concomitant resection of a solitary met
- 3) palliative for symptomatic locally advanced/metastatic RCC
- 4) cytoreductive prior to systemic therapy

What are the basic principles of a Radical Nx?

- early ligation of renal artery and vein
- removal of kidney outside Gerota's fascia } **most important aspect as ~25% have evidence of perinephric fat invasion**
- removal of ipsilateral adrenal gland } ONLY if extensive involvement of tumour or UP tumour
- performance of a complete regional lymphadenectomy } therapeutical value **controversial**

What are the limits of the regional lymphadenectomy performed with Radical Nx?

- start at crura of diaphragm just below SMA
- dissect along great vessels
- finish at origin of IMA
- watch out for origins of celiac axis and SMA
- identify cisternal chyli medial to right crus and ligate to prevent chylous ascites

Where are the potential sites of predictable retroperitoneal hemorrhage during Radical Nx?

- 1) lumbar veins } enters posterolateral aspect of IVC at each vertebral level
- 2) R gonadal vein } enters anterolateral surface of IVC
- 3) renal veins } lumbar veins course posteriorly into left renal vein and into IVC at level of R renal vein
→ can be particularly difficult to control
- 4) R adrenal vein } large, friable vein that inserts above right renal vein
- 5) IVC

What are the signs suspicious for IVC thrombus?

→ IVC thrombus occurs in 4-10% of presentations of RCC

→ "MAP a PLAN for the Vein"

- | | |
|--|---|
| - M urmur in R atrium (mass) | - A scites |
| - A bdo veins (superficial) dilated | - N on-functioning kidney |
| - P E | - V aricoele on R side, or one that doesn't collapse with recumbency |
| - P roteinuria | |
| - L ower limb edema | |

What are the different levels of IVC thrombus?

- renal vein
- infrahepatic
- intrahepatic
- suprahepatic

What is the order of IVC clamp placement and removal after thrombectomy?

→ placement

- 1) below thrombus
- 2) opposite renal vein
- 3) above thrombus

→ removal

- 1) above thrombus } ask for +ve pulmonary pressure
 } flushes out any fragments of thrombus left in IVC
- 2) opposite renal vein
- 3) below thrombus

***** below first to flush out air and fragments ????

How much of the IVC can be resected safely?

→ may be required when thrombus invades wall near entrance of renal vein

- **IVC can be safely narrowed by ~50%**
- further narrowing requires caval reconstruction with a free graft (pericardial or PTFE)

→ if extensive direct growth into wall of IVC, prognosis is poor, and must decide to resect or not

- resection of infrarenal IVC can be done safely } due to extensive collateral venous supply that develops
- resection of suprarenal IVC safe with R RCC } must ligate L renal vein medial to adrenal & gonadal tributaries, which will serve as collateral drainage of L kidney
 } may result in temporary ARF
- resection of suprarenal IVC NOT safe with L RCC } due to lack of collateral venous drainage from R kidney
 } R kidney can be auto-Tx'd or can use tumour-free strip of IVC and augment with a pericardial patch

What are the different ways to obtain control of the IVC for intrahepatic or suprahepatic thrombi?

- 1) temporary occlusion of suprahepatic intrapericardial IVC
 - temporarily occlude porta hepatis (Pringle's maneuver) and SMA to reduce hepatic venous congestion
 - tolerated only for 20 mins
 - NOT for thrombi that extend into the right atrium
- 2) cardiopulmonary bypass with deep hypothermic circulatory arrest
 - renal dissection & hemostasis carried out before bypass, which requires heparinization
 - can inspect entire lumen of IVC to ensure all fragments are removed
 - tolerated well for 40 mins } longer with adjunctive retrograde cerebral perfusion
- 3) caval-atrial shunt
 - veno-venous bypass useful for nonadherent supradiaphragmatic IVC thrombus
 - temporary occlusion of porta hepatis to prevent back-bleeding (Pringle's maneuver)

What are the potential complications after radical nephrectomy?

→ 20% post-op complication rate

→ 2% operative mortality rate

- 1) systematic
 - MI
 - CVA
 - PE/DVT
 - CHF
 - ARF
- 2) GI system
 - small bowel injury
 - duodenal injury
 - large bowel injury
 - liver lacerations (for R Radical Nx)
 - splenic injuries (for L Radical Nx)
 - pancreatic injury (tail for L Radical Nx)
 - SBO or LBO
 - ileus
 - incisional hernia
- 3) Pulmonary system
 - pneumothorax
 - tension pneumothorax
 - atelectasis
 - pneumonia
- 4) infections
 - wound infections
 - abscesses
 - lymphocele
- 5) local/incisional complications
 - incisional hernia
 - flank bulge (due to injury to intercostals nerve and muscle denervation)

What is the management of pancreatic leak/fistula after Radical Nx?

→ elevated serum amylase/lipase

→ send any drainage fluid for pH and amylase

→ CT scan may show fluid collection

- 1) perc drain of fluid collection
- 2) TPN
- 3) for prolonged drainage, may need surgical excision of fistulous track and construction of anastomosis between pancreas and Roux-en-Y limb of jejunum

What are the indications for a chest tube after pleural injury during a Radical Nx?

- 1) pneumothorax >10%
- 2) tension pneumothorax
- 3) symptomatic pneumothorax

PARTIAL NEPHRECTOMY FOR CANCER

What are the indications for Partial Nx for malignant disease?

- 1) if radical Nx would render patient anephric
 - bilateral RCC
 - RCC in solitary functioning kidney
- 2) functioning contralateral kidney but systemic disease that threatens future renal function
 - stones
 - chronic pyelo
 - RAS
 - VUR
 - DM
 - nephrosclerosis
- 3) single, small (<4cm), localized RCC with normal contralateral kidney
- 4) syndromic RCC (eg VHL)
- 5) select cases of Wilm's tumour or upper tract TCC
- 6) renal dysfunction

What are the contraindications for Partial Nx?

- tumour >4cm (changing now)
- tumour suggestive of renal TCC
- difficult central tumour
- +ve LNs
- renal vein or IVC thrombus

What is the pre-op w/u prior to a Partial Nx?

- hx and P/E
- bloodwork } cbc, lytes, creatinine, LFTs, Ca profile, ALP, coags
- triphasic CT abdo/pelvis
- CXR } chest CT if abN or if symptoms
- bone scan } only if symptomatic or elevated ALP

What are the basic principles of Partial Nx for malignant disease?

- vascular control
- avoidance of ischemic renal damage
- complete tumour excision with free margins
- precise closure of collecting system
- careful hemostasis
- closure or coverage of renal defect

What are the steps taken to prevent renal ischemic injury during Partial Nx?

- in situ renal hypothermia } ice slush for minimum 10-15 mins
 - } need to cool renal core to ~20C
- mannitol given 5-10 mins before temporary renal artery occlusion
- no systemic or regional anticoagulation needed

What are the different ways of performing a Partial Nx for malignant disease?

- 1) simple enucleation } higher risk of residual disease
 - } only used in occasional VHL patients
- 2) polar segmental Nx } ligation of polar apical or basilar branch
- 3) wedge resection } best w/ temporary renal artery occlusion + surface hypothermia
- 4) transverse resection (hemi-Nx) } avoid injury to posterior segmental branch, which may occasionally supply basilar renal segment
- 5) extracorporeal Partial Nx + renal autoTx } leave ureter attached when possible

What are the main advantages & disadvantages of extracorporeal Partial Nx + autoTx?

- advantages } optimum exposure
- } bloodless surgical field
- } ability to perform a precise operation w/ maximum conservation of renal parenchyma
- disadvantages } longer OR time
- } need for vascular and ureteral anastomoses
- } increased risk of temporary and permanent renal failure

How successful is Partial Nx for RCC?

- equivalent to Radical Nx for T1a tumours
- 5yr cancer-specific survival rates at ~90%
- **risk of local recurrence is ~5%** } likely manifestation of undetected micro multifocal RCC
- } stage dependent

What are the potential complications after a Partial Nx?

- overall rate <5%
- intra-op } - hemorrhage
- adjacent organ injury
- ureteral injury
- pleural injury
- early post-op } - **urinoma/urinary fistula (most common)**
- ureteral obstruction (clots)
- renal abscess
- delayed bleeding
- pneumothorax
- ileus
- SBO
- MI/DVT/PE
- UTI/pyelonephritis
- late post-op } - AV fistula
- renal failure (most common in solitary kidney)
- permanent in <5% of solitary kidneys
- ureteral stricture/UPJO
- HTN
- hernia
- recurrence of RCC

What are the RFs for development of a urinary fistula?

- central tumours
- size >4cm
- need for major reconstruction of collecting system
- extracorporeal surgery

What is the recommended post-op f/u after Partial Nx?

- f/u in 4-6weeks with serum creatinine and IVP (U/S if impaired renal function)
- surveillance schedule tailored to stage
- Hx, P/E, and creatinine, ALP, Ca, lytes, LFTs qyearly
- qyearly 24hr urinary protein after Partial Nx in solitary kidney
- CXR qyearly if ≥pT2 disease
- abdo/pelvis CT q2yrs for pT2 disease } more frequent for higher stage disease

What is hyperfiltration nephropathy?

- proteinuria, glomerulopathy, and progressive renal failure
- if >50% reduction in overall renal mass, risk of hyperfiltration nephropathy is high
- if proteinuria (>150mg/day) then treat with low-protein diet + ACE inhibitor

PARTIAL NEPHRECTOMY FOR BENIGN DISEASE

What are the indications for Partial Nx for benign disease?

- 1) hydronephrosis with atrophy or atrophic pyelo in a duplicated renal segment
- 2) calyceal diverticulum complicated by infection or stones
- 3) stone disease with obstruction of LP calyx or segmental parenchymal disease w/ impaired drainage
- 4) renovascular HTN due to segmental parenchymal damage or non-correctable branch renal artery disease (rare now given advances in renovascular reconstruction)
- 5) trauma with irreversible damage to a portion of the kidney
- 6) benign tumours (AML, oncocytoma)

What is the preferred approach for a Partial Nx for benign disease?

- extraperitoneal flank incision } except for renal trauma, which is best approached via abdo incision
 → can excise and reflect renal capsule for later use in covering renal defect

What are the basic principles of Partial Nx for benign disease?

- vascular control
 - avoidance of ischemic renal damage
 - precise closure of collecting system
 - careful hemostasis
 - closure or coverage of renal defect
- } similar to principles for Partial Nx
for malignant disease

RENAL ARTERY RECONSTRUCTION

What are the main categories of renal artery disease?

- | | |
|-----------------------------|---|
| 1) atherosclerosis } 80% | 5) neurofibromatosis } rare |
| 2) fibrous dysplasia } 20% | 6) extrinsic obstruction of renal artery } rare |
| 3) arterial aneurysm } rare | 7) middle aortic syndrome } rare |
| 4) AV fistula } rare | 8) renal artery thrombosis or embolism |

What are the main indications for surgical intervention for renal artery disease?

- HTN
- **preservation of renal function**
- **prevent rupture of aneurysm**

What are the options for intervention for renal artery disease?

- 1) percutaneous transluminal angioplasty (PTA) } ideal for isolated renal artery stenosis
- 2) stenting } (fibrous dysplasia or atherosclerosis)
- 3) surgical revascularization } still definitive treatment of choice for
 - } branch renal artery disease
 - } ostial atherosclerotic lesion
 - } arterial aneurysm
 - } failed endovascular therapy

What are the factors to consider before offering surgical intervention for renal vascular disease?

- causal relationship of renal vascular disease to HTN
 - not always related
 - renal artery disease more common than renovascular HTN
- adequacy of BP control with meds
- natural hx of untreated renal vascular disease (risk of renal impairment)
- medical condition of patient
- known results of intervention of choice

Indications for Treatment

What are the features suggestive of true renovascular HTN? } } } A FARMERSS BP

→ symptoms are rare, except flank pain related to segmental infarction or arterial dissection

→ renin-mediated

- Age } onset at age <30yrs or >55yrs (fibrous dysplasia or atherosclerosis)
- Family hx is negative } +ve FmHx suggests essential HTN
- Atherosclerosis (CAD, CVD, carotid disease, etc)
- Renal deterioration with ACE inhibitor
- Medication refractory, or suddenly worse
- Extreme HTN (accelerated, malignant HTN or HTN'sive crises)
- Retinopathy from HTN (grade 3 or 4)
- Smokers } higher incidence of smoking in RVH & FD than with essential HTN
- Sudden onset and shorter duration of HTN is suggestive of RVH } better chance of cure
- Bruit (upper abdominal)
- Pulmonary edema episodes

What lab tests are suggestive of RVH?

- 1) proteinuria → usually mild; can also be from DM, glomerulosclerosis, etc
- 2) hypoK → highly suggestive of RVH with 2° hyperaldosteronism (~15% of RVH patients have hypoK)
- 3) azotemia + atherosclerosis → suggestive of renal arterial cause of HTN

What are some other tests that are used to assess for RVH & IN?

- | | |
|---|---|
| 1) functional studies (no anatomic info) | 2) anatomic studies (no functional info) |
| - plasma renin activity (PRA) } limited use | - IVP } no longer used |
| - captopril test | - Duplex U/S |
| - captopril renography } best predictor of surgical cure | - MR angio |
| | - spiral CT angio |
| - RVR assays } can localize ischemic kidney | - angiography } gold standard |
| | |
| | |
| | |
| | |

What are the indications for surgical intervention for renovascular HTN?

- 1) fibrous dysplasia } depends on type of fibrous dysplasia
 - **intimal fibroplasia** \ - associated w/ progressive obstruction
 - **perimedial fibroplasia** / - surgery to improve HTN and preserve renal function
- 2) renal artery aneurysms
 - **if >2cm and noncalcified** \ - especially of concern in pregnant women
 - **causing significant HTN** / (increased risk of rupture)
- 3) atherosclerotic renovascular HTN
 - **refractory to meds**
 - **worsening renal function due to advanced disease**

Fibrous Dysplasia

What are the different types of fibrous dysplasia?

- intimal (10%) } kids, adults
 - } smooth, focal stenosis in proximal renal artery
 - } associated with dissecting hematomas
- medial (80%) } women 25-50yrs
 - } string-bead appearance in distal 2/3 of main renal artery
 - } **no progression to occlusion**
 - } associated with micro-aneurysms
- perimedial (10%) aka "Girlie disease" } women 15-30yrs
 - } extensive collaterals
- true fibromuscular dysplasia (<2%) } very rare
 - } occurs in kids & young adults (similar to intimal FD)

How successful is surgical management of fibrous dysplasia?

→ **indicated for intimal and perimedial fibroplasias BUT NOT for medial fibroplasia**

- PTA } 90-95% success rate for main renal artery
 } same results as with open surgery
- surgery } mainly for branch disease (30%) or for those who have failed PTA

Renal Artery Aneurysms

What are the 4 different types of renal artery aneurysms, according to Poutasse?

- 1) Saccular → **most common type (75%)**
 - occur at bifurcation of renal artery, so **branch involvement is common**
 - 25% bilateral or multiple aneurysms
 - may become involved w/ intramural calcification or atherosclerotic degeneration
 - may rupture spontaneously, may erode into renal vein or renal pelvis, and may form mural thrombus +/- emboli
- 2) Fusiform → occurs as **uniform dilatation of entire segment of renal artery**
 - actually a **post-stenotic dilatation**
 - more common in **young HTN'sive patients with FD**
 - **not calcified**
 - may become thrombosed
- 3) Dissecting → usually complication of renal arterial involvement w/ atherosclerosis, intimal or perimedial fibroplasia
 - results from a **tear in the internal elastic membrane of the renal artery**
 - blood flow through opening separates intima from rest of arterial wall
 - may result in arterial thrombosis + renal infarction or rupture + hemorrhage
- 4) Intrarenal → of mixed origin } may be congenital, post-traumatic, iatrogenic, neoplastic, or associated with polyarteritis nodosa
 - **usually saccular or fusiform +/- calcification**
 - have a **propensity for rupture**
 - can resolve if post blunt trauma or percutaneous renal Bx

List causes of renal artery aneurysm } } } "PICK ME MAMA"

- | | | |
|---------------------------------|------------------|------------------------------|
| - Polyarteritis nodosa | - Marfan's | - Medial FD (microaneurysms) |
| - Iatrogenic (eg PCNL, Bx, PNx) | - Ehler's Danlos | - Atherosclerosis |
| - Congenital | | - Mycotic (infection) |
| - Kawasaki's disease | | - AD PCKD |

What are the RFs for rupture of a renal artery aneurysm?

- 1) absent or incomplete calcification
- 2) size >2cm
- 3) coexisting HTN
- 4) pregnancy

List the indications for surgical removal of renal artery aneurysms } } } "WEBBERRR'S DIC"

- 1) **W**oman of childbearing age who is likely to conceive
- 2) **E**mbolization from thrombus with aneurysm on angio
- 3) **B**igger than >2cm + other RF for rupture
- 4) **B**P uncontrolled
- 5) **E**xpanding on imaging
- 6) **R**enal ischemia
- 7) functionally significant **R**AS
- 8) **R**uptured
- 9) **S**ymptoms (flank pain, hematuria)
- 10) **D**issecting aneurysm
- 11) **I**ncomplete **C**alcification

Renal AV Fistula

What are the 3 types of renal AVFs?

- 1) congenital → 25% of all renal AVFs
→ occur equally in M and F, manifesting late in adult life
→ **cirsoid or angiomatous** configuration with **multiple communications**
→ usually supplied by renal arterial branch of normal caliber
- 2) idiopathic → 5% of all renal AVFs
→ single communication
- 3) acquired → **most common type at 70%**
→ **single communication**
→ mostly due to renal Bx } others include RCC, renal trauma (blunt/penetrating), inflammation, renal Sx (Nx, PNx, PCNL)
→ often disappears spontaneously after several months

What is the epidemiology of congenital renal AVFs?

- usually present in 3rd or 4th decade
- more common in F (3:1) } **more common on R side**
- most commonly in UP (45%), least common in lower pole (25%)

What are the signs & symptoms of a renal AV fistula?

- renal bruit (75%)
- HTN (40-50%) } renin-mediated
- LV hypertrophy & high-output cardiac failure (50%)
- hematuria (75%)
- abdo or flank pain
- diminished or absent function in affected segment
- filling defect in collecting system (clot or encroachment by fistula)

What are the indications for surgery for a renal AV fistula? } } } “CHHERR”

- CHF
- HTN uncontrolled
- Hematuria
- Expanding lesion on imaging
- Retroperitoneal bleed (ruptured)
- Renal Insufficiency/failure

What are the options for management of a renal AV fistula?

- selective embolization
- balloon catheter occlusion
- vascular ligation
- nephrectomy
- partial Nx

Renal Artery Stenosis

What are RFs predictive of atherosclerotic RAS? } } } “A CCCP FAD” (*** HTN is not helpful ***)

- 1) higher Age
- 2) CAD
- 3) hx of CHF
- 4) elevated Creatinine
- 5) PVD
- 6) Female
- 7) progressive Azotemia after BP control with meds
- 8) DM

How successful is surgical management of atherosclerotic renovascular HTN?

→ only if **HTN refractory to meds** OR **worsening renal function** due to advanced vascular disease

- PTA } good result except for ostial atherosclerosis
- } high re-stenosis rate if used for ostial lesions
- endovascular stenting } better results for ostial lesions than PTA
- open surgery } best results for ostial lesions

Which patients with atherosclerotic renal artery disease are at risk for ischemic nephropathy?

→ development of IN from atherosclerotic renal artery disease is separate & distinct from RVH

- 1) high-grade stenosis (>75%)
- 2) involving entire renal mass (bilateral or disease in solitary kidney)
- 3) older age
- 4) diffuse extrarenal vascular disease

What are the features suggestive of ischemic nephropathy?

- 1) unexplained azotemia or if associated with ACE inhibitor use
- 2) diminished renal size
- 3) vascular disease in other sites (CVD, CAD, PVD)

What are the 5 signs of renal salvageability in complete occlusion RAS?

→ “Can Save GFR”

- Creatinine <350 g/L (US <4mg/dL)
- Size >9cm
- Glomeruli well preserved on Bx
- Function seen on nuclear scan or IVP
- Retrograde filling by collaterals seen on angiography

Pre-op Considerations

What are the main pre-op considerations prior to surgical intervention for renal artery disease?

- for atherosclerotic disease, screening & correction of significant extra-renal vascular disease
 (eg CAD, carotid disease)
- catheter angiography } assess & characterize lesion
- } assess & characterize surrounding vasculature in anticipation of possible
 extra-anatomic bypass procedures
- may need systemic heparinization
- consider staged procedure if B/L disease } more diseased artery first for renovascular HTN
- } larger kidney first for ischemic nephropathy
- consider secondary hyperaldosteronism for patients with renovascular HTN } watch for hypoK
- optimize renal perfusion } aggressive hydration and liberal use of mannitol

Aortorenal Bypass

What is the preferred method of surgical revascularization for renal artery disease?

- [illegible]

Alternative Bypass Techniques

What are the indications for simultaneous renal revascularization and aortic replacement?

- associated w/ significantly higher mortality rate (5-30%) cf renal revascularization Sx alone (~5%)
- **should ONLY BE CONSIDERED in patients with significant AAA or symptomatic aorto-iliac occlusive disease**

List the RF's for significant M&M after simultaneous renal revascularization + aortic replacement

- hx of CAD
 - ventricular hypertrophy
 - elevated creatinine
 - diffuse PVD
 - bilateral renal artery disease
- } strongly consider alternative bypass options

List the alternative bypass options for renal revascularization

- hepatorenal bypass
- splenorenal bypass
- thoracic aortorenal bypass
- iliorenal bypass
- mesenterorenal bypass
- extracorporeal microvascular branch renal artery reconstruction + autoTx

Describe the alternative bypass options for renal revascularization, other than aortorenal bypass?

1) hepatorenal bypass

- most commonly use interposition saphenous vein graft from end of renal artery to side of **common hepatic artery**
- must ensure unobstructed celiac and hepatic arteries prior to surgery
 - usually not good option in older pts w/ diffuse abdominal atherosclerotic dz
- preferred option for pt with **troublesome aorta that needs R renal revascularization**
- liver has dual blood supply: 80% portal vein and 20% hepatic artery
- ensure normal LFTs prior to surgery
- GB susceptible to ischemia, may necrose if blood supply from R hepatic removed
 - use left hepatic when possible OR perform cholecystectomy

2) splenorenal bypass

- must ensure unobstructed celiac and **splenic arteries** prior to surgery
 - usually not good option in older pts w/ diffuse abdominal atherosclerotic dz
- preferred option for pt with **troublesome aorta that needs L renal revascularization**
- no need to remove spleen as it gets collaterals from short gastrics and gastroepiploics
- ADVANTAGES:
 - operation done well away from aorta
 - single vascular end-to-end anastomosis
 - autogenous vascular graft

3) thoracic aortorenal bypass

- lower thoracic imaging needed prior to surgery to ensure unobstructed vasculature
- used in pts w/ **significant abdominal aortic atherosclerosis, celiac artery stenosis, and no indication to replace abdominal aorta**
- subdiaphragmatic supraceliac and descending thoracic aorta often free of disease
- most commonly use interposition saphenous vein graft
- ADVANTAGES:
 - thoracic aorta healthy and provides good inflow
 - don't need to fully occlude thoracic aorta so distal flow preserved and no need for heparinization
 - avoids aortic cross clamping
 - no need for synthetic graft
 - limited renal ischemia

- employed because of abdominal aortic atherosclerosis or previous aortic surgery
- IN improved in ~40%, stable in ~45%, deterioration in ~15%
- best results seen in group with pre-op creatinine <180 µg/L (<2 ng/mL)
- HTN cured in ~15%, improved in ~60%, unchanged in ~25%

Complications

What are the potential complications of renal vascular surgery?

- mortality } minimal in patients with fibrous dysplasia or aneurysm (usually young)
 - } 6-10% in patients with atherosclerotic renal artery disease (older, sicker)
 - } reduced mortality with pre-op correction of CAD or CVD, avoidance of B/L renal surgery, and avoidance of surgery on a diseased aorta
- HTN } common in early post-op period
 - } may persist for several wks after surgery → need to do renal scan to confirm patency
- hemorrhage } usually due to poor surgical technique
 - } late hemorrhage can occur weeks, months, or even yrs after
 - infected suture line
 - rupture of non-infected false aneurysm at anastomotic site
 - erosion of prosthetic graft into GI tract
- renal artery thrombosis } occurs in <5%
 - } usually occurs within first few days post-op and is due to poor technical performance (persistent or sudden HTN & elevated creatinine)
 - } RFs include post-op hypoTN, hypercoagulable state and hypovolemia
- renal artery stenosis } occurs <10%
 - } late complication
 - } due to faulty sutures, intimal trauma, incomplete excision of primary vascular disease, wide disparity in vessel size, dissection of a distal intimal flap, torsion, angulation, kinking
- renal artery aneurysm } occurs in <10%
 - } more common in kids
 - } may be associated with stenosis distal to aneurysm
 - } more common with use of gonadal vein grafts so these are not used
- aortic complications } aortic thrombosis, distal embolization, etc
 - } aortic dissection from clamping and unclamping
- visceral complications } injuries to spleen, pancreas during alternative bypass techniques
 - } GB necrosis with ligation of right hepatic artery during hepatorenal bypass
- ARF } can be prevented in most cases
 - } avoid warm ischemia >30 minutes

What is the management of post-op renal artery thrombosis?

- **emergency re-exploration + thrombectomy or graft revision if kidney viable**
- intra-arterial infusion of streptokinase (risk of bleeding)
- percutaneous thrombectomy (not good option with fresh anastomosis)
- Nx if no longer viable

What is the management of post-op renal artery stenosis?

- PTA stenting
- re-operation

MISCELLANEOUS RENAL SURGERY

Open Renal Bx

When is open renal Bx preferred over percutaneous Bx?

- 1) solitary kidney
 - 2) coagulopathy
 - 3) atypical renal anatomy
 - 4) need for adequate tissue for study
 - 5) any factor that may increase the risk of a closed Bx
 - 6) failed percutaneous Bx
- R kidney preferred due to lower location
→ extraperitoneal flank or lumbodorsal approach preferred

List 5 ways to Bx the kidney.

- open
- laparoscopically
- percutaneously
- ureteroscopically
- transvenously

Simple Renal Cysts

What are the indications for surgical management of simple renal cysts?

- 1) large cyst that causes obstruction
- 2) significant pain with documented improvement after perc drainage
- 3) if Dx uncertain and need to r/o atypical tumour

Open NT Insertion

What are the indications for open NT insertion?

- 1) atypical renal anatomy making perc access difficult
 - 2) minimally dilated upper tract
 - 3) intra-operatively during reconstructive procedures (eg pyeloplasty or ureterocalicostomy)
- extraperitoneal flank incision preferred
→ NT passed retrogradely, via pyelotomy, through calyx along Brodel's avascular plane in parenchyma
→ should leave drain near pyelotomy site

PCKD

What are the indications for bilateral Nx for PCKD?

- 1) hx of significant bleeding
 - 2) hx of renal infections
 - 3) massively enlarged kidneys that may interfere with placement of renal Tx
 - 4) hx of significant pain from obstruction or bleeding
- anterior bilateral subcostal or midline transperitoneal incision preferred

What is Rovsing's operation?

- **multiple cyst punctures & unroofing of cysts for PCKD**
- does not improve renal function
 - does not prevent further deterioration
 - can provide long-term pain relief in symptomatic patients

Horseshoe kidney

What are the indications for isthmusectomy for a horseshoe kidney?

- 1) ureteral obstruction or UPJO with recurrent stones
- 2) ureteral obstruction or UPJO with recurrent infections
- 3) obstruction with evidence of hydronephrosis and renal dysfunction
- often done in conjunction with correction of obstruction of collecting system
- anterior subcostal extraperitoneal approach preferred
- **RARELY EVER DONE NOW**

Renal Pelvic TCC

What are the indications for open pyelotomy and tumour excision of upper tract TCC?

- 1) non-invasive TCC of renal pelvis in solitary, functioning kidney
- 2) bilateral non-invasive TCC of renal pelvis
- after tumour resection, perform pyeloscopy to examine rest of collecting system
- alternative options include partial Nx or endourologic procedures

Renal Artery Thrombosis or Embolism

What are the causes of renal artery THROMBOSIS (CHART)? }}} “FAT Pig SAT UP”

- 1) **F**D of renal artery
- 2) **A**therosclerosis of aorta or renal artery
- 3) **T**rauma
- 4) **P**olycythemia
- 5) **S**yphilis
- 6) **A**ngiography (aortic or renal artery)
- 7) **T**hromboangiitis obliterans
- 8) **U**mbilical artery catheterization in neonates
- 9) **P**olyarteritis nodosa

What are the causes of renal artery EMBOLISM (CHART)? }}} “MAP TO embolism AVE”

- 1) **M**I (acute)
- 2) **A**-fib
- 3) “**P**aradoxical” embolism → presence of ASD/VSD
- 4) **T**umour (cardiac)
- 5) **O**pen heart surgery
- 6) **A**neurysm } saccular renal artery aneurysm
 } ventricular aneurysm
- 7) **V**alvular **V**egetations (aseptic)
- 8) bacterial **E**ndocarditis

What are the main complications of U/S-guided renal Bx?

- significant hemorrhage (5%)
- inadequate tissue (5-20%)

What are the indications for Lap renal Bx?

- 1) failed percutaneous needle or transjugular Bx } eg morbid obesity, multiple B/L cysts
- 2) anatomic variations
- 3) risk of bleeding complications
 - retroperitoneal approach
 - 5mm toothed Bx forceps
 - hemostasis with argon beam coagulator

What are the potential complications of Lap renal Bx?

- overall complications rate is 5-10%
- bleeding } ensure slow resumption of anticoagulants when needed
- colon injury (rare)

SIMPLE NEPHRECTOMY

What are the indications & contraindications for Lap Simple Nx?

→ INDICATIONS

- renovascular HTN
- symptomatic ARCD in ESRD pts
- nephrosclerosis
- symptomatic AD PCKD
- chronic pyelo
- reflux or obstructive nephropathy
- MCDK
- chronic pain of renal origin refractory to conservative measures

→ CONTRAINDICATIONS

- absolute } uncorrected coagulopathy
- } untreated infection
- } hypovolemic shock
- relative } complex intra-abdo surgery
- } ileus or SBO
- } ?XGP
- } ?renal TB

What is the evidence for the use of local anesthetic in the trocar sites?

- **double-blind, RCT showed benefit with use of 0.5% bupivacaine before port placement**
- less post-op narcotic use at all time points
- Kharia and Wolf '04

How many trocars are used?

- usually 3 to 5
- 12mm port at level of umbilicus, lateral to rectus } for clip applier, etc
- 10-12mm port at umbilicus } for camera
- rest are 5mm ports

Describe the main steps of a Simple Nx?

- obtain access
- examine peritoneum
- mobilize colon
- dissect ureter } ureter alone on R, ureter and gonadal vessels on L
- dissect out renal hilum } use ureter as guide and march up to hilar vessels
- secure and ligate renal vessels } renal artery first
- mobilize upper pole } preserve adrenal gland
- mobilize kidney from lateral and posterior attachments to abdo wall
- organ removal } intact through enlarged incision or after morcellation

RENAL CYSTIC DISEASE

What is the Bosniak classification of renal cysts?

→ originally based on CT findings

- Bosniak I } thin wall, no septations, 0-20HU pre-contrast
- Bosniak II } thin wall, no or few thin septations, minimal calcification, 0-20HU
- Bosniak III } thicker wall, multiple septations, moderate calcification, 0-20HU
 → may have mild enhancement of septations
- Bosniak IV } thick wall, thick septations, coarse calcifications, >20HU pre-contrast,
 and +VE enhancement of solid component

What are the indications for Lap renal cyst surgery?

- cyst marsupialization, decortication, unroofing } transperitoneal VS retroperitoneal approaches
- pain } 1st line therapy often needle aspiration +/- sclerosis
 } resolution of symptoms after drainage and return of symptoms with reaccumulation
 increases likelihood that Lap surgery will be successful
- infections
- bleeding/hematuria
- compression of collecting system
- HTN
- exploration of complex cysts

How successful is Lap surgery for symptomatic renal cysts?

- 80-90% are asymptomatic

What are the important steps in Lap renal cyst surgery for complex cysts?

- prepare patient for possible partial or radical Nx
- send cyst capsule for frozen section } sending cyst fluid for cytology usually of limited value
- send normal parenchyma at edge of resection for frozen section
- fulgurate edges if benign; avoid central portion for risk of entering collecting system
→ can use ureteral catheter + indigo carmine if close to collecting system

What is the role for Lap renal cyst decortication for AD PCKD?

- for symptomatic AD PCKD with adequate renal function, many cysts must be drained & marsupialized to relieve pain (often >100)
- for symptomatic AD PCKD and renal failure, can perform Lap simple Nx, but will require aspiration of many cysts to decrease size of kidney to see hilar vessels
→ usually doesn't bleed that much
→ due to distorted anatomy, need to watch for collecting system

What are the main complications following Lap renal cyst decortication?

- urinoma
- bleeding

How successful is Lap cyst decortication for symptomatic AD PCKD?

- >70% are pain free
- occasional improvement of HTN
- no significant decrease in renal function

How successful is Lap Nx for symptomatic AD PCKD and renal failure?

- higher complication rate due to difficult dissection
- higher rate of conversion to open surgery (~15%)

NEPHROPEXY

What is nephroptosis?

- inferior displacement of kidney by >5cm when patient moves from supine to erect position
- often in young, thin women
- causes symptoms } eg Dietl's crisis
 - severe colicky flank pain
 - chills
 - oliguria
 - nausea
 - tachycardia
 - transient hematuria

What are the indications for nephropexy?

- symptomatic nephroptosis } hx of pain in erect position
 - } diminished renal blood flow on Doppler in erect position
 - } documented obstruction on IVP or renal scan in erect position
 - } documented descent of kidney by ≥ 2 vertebral bodies
- ~80% improvement in pain

Describe the main steps of a nephropexy?

- mobilize lower, lateral and posterior attachments
- suture upper pole to fascia over psoas or quadratus lumborum
- can also suture anterior capsule to subhepatic parietal peritoneum
- transperitoneal or retroperitoneal approaches

PYELOLITHOTOMY AND URETEROLITHOTOMY

What are the indications for Lap Pyelolithotomy or Lap Ureterolithotomy?

- failed ESWL or PNL or ureteroscopy
- unusual anatomy (eg pelvic kidney)
- stones resistant to fragmentation (eg cystine stones)
- repair of concomitant UPJO and renal stones
- **VERY LIMITED INDICATIONS**

CALYCEAL DIVERTICULECTOMY

What are the management options for calyceal diverticula with stones?

- open/lap marsupialization + stone removal + fulguration of diverticulum
- antegrade } PNL + dilation of diverticular neck or ablation of diverticular cavity
- retrograde } ureteroscopy + dilation of diverticular neck
- partial Nx

What are the indications for Lap marsupialization and fulguration of a calyceal diverticulum?

- large peripheral diverticula
- medial diverticula near hilum
- anterior diverticula

Describe the main steps of Lap surgery for a calyceal diverticular stone?

- open thin parenchyma over tic & remove stones intact } can help identify tic by looking for "dimpling" on surface of kidney or the presence of dense adhesions over the tic
- fulgurization of lining of cavity to prevent recurrence
- collecting system can be closed with sutures } methylene blue can be used to identify urine

LAPAROSCOPY FOR RENAL MALIGNANCY

What is the risk of port site seeding for GU malignancies?

- few case reports of port site seeding for RCC (4), TCC (7), adrenal carcinoma & PCa after pelvic LND
- RCC port site seeding cases (4) were associated with morcellation (2) and removal of intact specimen without entrapment bag (2)
- risk of wound mets after open radical Nx for RCC is ~0.4%
- port site seeding rates higher for gen sx (colon and gallbladder)

What are the recommendations to prevent port site seeding during Lap surgery for malignancy (CHART)?

- avoid resection & excision of tissue in presence of carcinomatosis
- isolate ascitic fluid to be sent for cytology from all wounds
- minimize direct tumour handling to prevent iatrogenic tumour violation
- ensure wide en-bloc dissection of tumour and surrounding tissues
- place all tissues within an impermeable Lap sac before morcellation or tissue extraction
- re-drape port sites at time of tissue removal
- remove all possible contaminated instrumentation from newly draped-off operative field
- change surgical gloves before formal peritoneal closure

RETROPERITONEAL RADICAL NEPHRECTOMY

What are the potential advantages of retroperitoneal Lap Radical Nx over transperitoneal?

- avoids adhesions associated with previous extensive intra-abdominal surgery
- more direct access to renal vessels for early control

What are the potential disadvantages of retroperitoneal Lap Radical Nx cf transperitoneal?

- small working space
- difficult if previous renal surgery or infections disease processes (TB, XGP, pyelo, etc)

Describe the main steps of a Retroperitoneal Lap Radical Nx?

- obtain access
 - initial incision made 2cm below tip of 12th rib, between the ASIS
 - finger dissect space in retroperitoneum } feel for psoas and lower pole of kidney
 - balloon dilate retroperitoneal space below kidney to 600-800cc
 - posterior trocar placed and used to help mobilize peritoneum medially
 - 2nd anterior trocar placed
- identify ureter and follow up to lower pole } use psoas tendon as guide
 - } aorta and IVC are just medial to ureter
- identify renal vessels } renal artery usually encountered first (watch for lumbar vein on left)
 - } identify renal vein next (**on right, make sure not looking at IVC**)
- mobilize lower pole and divide gonadal vessels
- mobilize kidney anterior also
- complete mobilization of kidney from superior attachments } +/-adrenal sparing
- entrap and extract specimen

What are the success rates of Retroperitoneal Lap Radical Nx?

- similar outcomes compared to transperitoneal approach with same benefits over open sx
- comparable complication rate, analgesic requirements, length of hospital stay, time to return to normal activity
- 2 prospective randomized trials comparing transperitoneal vs retroperitoneal
 - no major differences

What is the pre-op evaluation prior to transperitoneal Lap Radical Nx?

[illegible]

- “Bad Reasons CHAMP” } bowel obstruction, retroperitoneal abscess, coagulopathy, hematoma, abdo wall infection, etc

- tumour characteristics
- surrounding vessels

} routine pre-op (renal scan prn)

- mobilize the ureter } on right, look for gonadal vein inserting into IVC and leave posterior
- } on left, gonadal vein can be elevated with the ureter

- entrap and extract specimen

- similar complication rate (15-20%)

HAND-ASSISTED RADICAL NEPHRECTOMY

What are the potential advantages of a hand-assisted Lap Radical Nx (HALN)?

- decreases the learning curve of Lap sx
- useful when difficult dissection anticipated
- early control of bleeding
- tactile sensation
- may be beneficial when performing bilateral renal surgery } midline hand port
- can place intra-abdominal sponge to help with dissection and absorption of blood
- inserted hand can help in closing trocar sites

What are the potential disadvantages of a HALN?

- needs larger incision
- may be difficult to maintain adequate pneumoperitoneum
- limited as to the placement of the hand-port
- can cause discomfort to surgeon's hand

What characteristics can make HALN difficult?

- obese patients
- R-sided tumours
- prior surgery
- tumours near the renal hilum

What are the relative contraindications to HALN?

- large tumours (>15cm)
- hx of peritonitis
- extensive abdo surgery
- IVC thrombus
- ipsilateral abdo wall stoma

Describe some of the differences with HALN?

- can transect ureter earlier because hand can be used to elevate kidney
- ensure hand doesn't violate Gerota's fascia
- careful handling of adrenal as it is fragile } finger can be used to dissect plane b/w adrenal & kidney for adrenal-sparing sx
- can palpate hilar vessels to aid in dissection

What are the success rates of HALN?

- similar cancer survival outcomes as Lap Radical Nx
- shorter OR time
- more abdo pain and more wound complications (4% hernia rate)

NEPHRON-SPARING SURGERY

What are the indications for Lap Partial Nx?

- peripheral, well-circumscribed lesions <4cm in patient with N renal function & N contralateral kidney
- solitary kidney
- bilateral RCC
- significant renal insufficiency
- patients with genetic predisposition to recurrent RCC
eg VHL, TS, HPRCC

Describe the main steps in a Lap Partial Nx?

- obtain access
- mobilization of kidney similar to Lap Nx
- enter Gerota's fascia } attempt to keep layer of perinephric fat over tumour
- inspect rest of renal capsule for satellite mets
- renal vessel control can be done with lap bulldogs or Satinsky clamp
 - both artery and vein VS artery only
 - with or without intrarenal or extrarenal cooling
 - advances in technology (eg microwave coagulators) may mean no need for renal ischemia
- can add intraop U/S to assess margins
- excision of lesion performed with scissors, ultrasonic shears or endoscopic scalpel
- absorbable intra-corporeal sutures used to close defects into collecting system
 - can use ureteric catheter + methylene blue to identify collecting system violation
- can use several techniques to achieve hemostasis in open renal defect
 - gelfoam
 - surgical bolster } may see air on early post-op imaging (NOT gas-forming infection)
 - argon beam coagulation
 - Tisseel
 - Floseal
- drain placement post-op (discretion of surgeon)

What is the role of renal cooling?

- extrarenal cooling (ice slush in endocatch bag) and intrarenal cooling (ice-cold saline infusion via ureteral catheter or continuous perfusion of 4°C RL into clamped renal artery)
- benefits debatable

What is the role of Retroperitoneal Lap Partial Nx?

- small working space makes suturing difficult
- good access to renal vessels

What is the role of hand-assisted Lap Partial Nx?

- can often aid in vascular control } can use compression technique without hilar occlusion
- must have access to hilum as significant bleeding may occur

What other techniques are available to facilitate hemostasis?

- in-situ Lap ablative techniques may decrease bleeding enough to avoid renal ischemia
- Lap RFA prior to excision
- Lap Microwave tissue coagulation (MTC) prior to excision

What are the success rates of Lap Partial Nx?

- renal ischemia is major issue
- most studies show feasibility and low morbidity of Lap Partial Nx in treatment of RCC

What are the potential complications after Lap Partial Nx (CHART)?

- bleeding/hemorrhage
- urinoma
- trocar site infection
- pneumothorax/tension pneumo
- pulmonary edema
- completion nephrectomy
- renal insufficiency
- tumour fragmentation
- +ve margins

LAPAROSCOPIC ABLATIVE TECHNIQUES

What are the indications for Lap ablative therapies of renal tumours?

- solitary kidney
- bilateral renal tumours
- renal insufficiency
- patient request
- tumours adjacent to bowel/vital organs (perc not good option)
- genetic predisposition to recurrent RCC eg VHL
- significant co-morbidities
- unable to access via percutaneous access eg hilar lesions

Cryoablation

What are the success rates of Lap Cryoablation?

- renal tissue **temp < -20°C required** to create tissue necrosis
- need to extend ice ball ~1cm beyond edge of lesion
- post-op surveillance based on imaging
- cancer-free survival is ~95%
- ~5-7% local recurrence or inadequate treatment

What are the 4 histologic zones of damage seen after cryoablation?

- 1) complete necrosis (centre)
- 2) inflammatory infiltrate
- 3) hemorrhage
- 4) fibrosis and regeneration (outer edge)

What are the potential complications of Lap Cryoablation?

- urinary fistula formation
- post-treatment hemorrhage
- injury to adjacent organs (renal pelvis, bowel, liver, etc)

How are patients assessed after cryoablation?

- MRI } non-enhancement after Gad (most cryolesions DO NOT resolve completely)
 } cryolesion is isointense to normal parenchyma on T1 and hypointense on T2
- CT } can also be used to follow cryolesions

RFA

What are the success rates of Lap RFA?

- renal tissue **temp >60°C required** to induce coagulative necrosis
 - no way of monitoring ablation intra-op
 - post-op surveillance based on imaging
 - ~90-95% disease-free survival
 - ~10% rate of recurrence/incomplete treatment
- \ f/u data not as long
/ as for cryoablation

What are the potential complications after Lap RFA?

- ~5% overall complication rate specific to RFA (not related to Lap approach)
- UPJ obstruction
- hemorrhage
- ileus
- urinoma
- pain or paresthesia at ablation probe insertion site

How are patients assessed after RFA?

- CT } lack of enhancement considered a success
 } endophytic tumours develop low-density, nonenhancing, wedge-shaped defect w/ fat infiltration between ablated tissue and normal kidney
- } exophytic tumours maintain their shape but do not enhance

COMPLICATIONS OF LAPAROSCOPIC RENAL SURGERY

What are the complications of Lap Renal Sx?

- ~5-10% overall complication rate
- ~10% conversion rate (most cases related to Nx for infectious causes)
- 1) positioning-related complications
 - brachial nerve injury
- 2) access and insufflation-related complications
 - intraperitoneal organ injury } vessels, bowel, liver, spleen
 - epigastric vessel injury } can get abdo wall hematoma or major hemorrhage
 - tension pneumothorax
 - subcutaneous emphysema } can lead to pneumomediastinum or pneumothorax
 - gas embolism } mill-wheel murmur, hypoTN, tachycardia, evidence of pulmonary HTN
 - } usually from trocar injury or open venous sinus
- 3) intra-op complications
 - bleeding/hemorrhage } hilar dissection, right gonadal vein, lumbar veins, mesentery
 - vascular injury } reports of complete transection of IVC during retroperitoneoscopic Nx
 - } stapler malfunction/failure (~2%)
 - violation of tumour
 - adjacent organ injury } colon, small bowel, liver, duodenum, diaphragm, spleen, pancreas, adrenal gland, etc
 - volume overload
- 4) post-op complications
 - wound infection
 - pneumonia
 - unrecognized bowel injury (~0.1%) } 60% small bowel and 50% from cautery
 - } presents as persistent or increased trocar site pain close to site of injury
 - urine leak (partial Nx)
 - MI/DVT/PE/stroke
 - chronic pain/thigh numbness (nerve injuries)
 - orchialgia

How do patients with unrecognized bowel injury present?

- persistent and increased trocar site pain at site closest to bowel injury
 - low-grade fever
 - low or normal WBC count
 - persistent bowel sounds
 - nausea
 - diarrhea
 - anorexia
- can rapidly deteriorate if not recognized and treated quickly

List complications of CO₂ pneumoperitoneum at 15cm H₂O.

- hypercapnia
- respiratory acidosis
- arrhythmias
- subcutaneous emphysema
- pneumothorax
- pneumomediastinum/pneumopericardium
- barotrauma
- CO₂ embolus
- decreased urine output

List clinical signs of gas embolism?

- often due to puncture of blood vessel or organ with Veress needle or large open veins
- acute CV collapse
- cyanosis
- sudden decline in O₂ sat's (hypoxia)
- arrhythmias
- initial increase followed by marked decrease in end-tidal CO₂
- "mill-wheel" murmur
- pulmonary edema
- foaming of blood sample drawn by anesthesia

What is the management of gas embolism?

- communicate with anesthesia
- immediate stoppage of insufflation & desufflate abdomen
- LLD (right-side up) + Trendelenburg } to minimize R ventricle outflow problems
- hyperventilate with 100% O₂
- advance central line into right heart and try to aspirate } rarely successful
- hyperbaric O₂ & cardiopulmonary bypass reported

Chapter #52 – Ablative Rx of Renal Tumours

RATIONALE FOR ENERGY ABLATIVE THERAPY

What is the appeal of energy ablative therapy for renal masses?

- increase in incidentally detected small renal masses
 - 20% of tumours $\leq 4\text{cm}$ are benign
 - small renal masses grow slowly (0.22-0.54cm per yr)
- high comorbidity associated with partial Nx
- kidney is easily accessible laparoscopically or percutaneously

DEFINING SUCCESSFUL ABLATION

How is successful ablation defined?

- complete loss of contrast enhancement on f/u imaging
 - residual viable tumour has been shown in non-enhancing lesions post-RFA (Rendon et al '02)
- progressive shrinking after therapy
 - however, may take months and less pronounced after RFA
- normal Bx's post therapy
 - however inaccuracy of Bx's have been shown, especially of small lesions

CRYOABLATION

How does cryoablation work?

- rapid freeze-thaw cycles } **cell death at temp $< -20^\circ\text{C}$**
- ice ball generated at tip of probe } can be monitored real-time
- tissue necrosis occurs by direct damage on a cellular level and indirect damage from malperfusion during the thawing process
- secondary reperfusion injury also results in cell death
- predictable cell death occurs up to a point $\sim 5\text{mm}$ from the edge of the iceball

What factors predict better cell death?

- lowest temp reached (margins are usually -40°C)
- total time at subzero temps
- speed of freezing
- # of freeze-thaw cycles
- size and area of contact of cryoprobe

How successful is cryoablation?

- lap cryo } $\sim 5\%$ failure rate
 - } failures mainly in tumours $> 3\text{cm}$ and centrally located tumours
 - } minimal complications, avg stay $< 2\text{days}$
- perc cryo } 15% failure rate with avg f/u of 24 months
 - } minimal complications, avg stay $< 24\text{hrs}$
- mainly indicated for **lesions $< 3\text{cm}$ in diameter that are peripherally located**
- slightly higher complications after perc cryo .. but overall low
- major complications in only $\sim 2\%$ (hemorrhage and urinary fistula)

RFA

How does RFA work?

- radiofrequency electric current delivered through needle electrode (bipolar or monopolar)
- **heating >60C results in instantaneous & irreversible coagulation necrosis**
- dynamically expanding sphere of heat-induced tissue damage created outward from electrode
→ can't be monitored reliably in real-time

What factors predict better cell necrosis?

- close distance to electrode } 105C near tip
- current application that isn't too high or too rapid } charring occurs if too high or too fast
 } heating process stops
- use of multi-tine RF probes
- cooled electrode } avoids rapid increase of impedance and so more energy is deposited
- tumour away from large vessels } conducts energy away from heat sphere

How successful is RFA?

- ~10% failure rate
 - failure rate higher when tumour >4-5cm and centrally located
 - low complication rate } mostly minor
- ideal for **small, exophytic, peripheral tumours**

What are the potential complications after RFA?

- perinephric hematoma
- urine fistula
- bile fistula
- pancreatic pseudocyst
- ureteric stricture
- incomplete treatment
- bowel injury

MICROWAVE ABLATION

How does microwave ablation work?

- microwave thermotherapy via needle
- can reach tissue **temp only as high as ~60C**
 - usually requires multiple needle placements and repeat treatments
- cone-shaped area of coagulative necrosis produced between needle tip & circle electrode at base
- main use is to facilitate hemostasis at partial resection of parenchymal organs w/o ischemia

INTERSTITIAL LASER COAGULATION

How does interstitial laser coagulation work?

- bare-tip laser fiber used for focal tissue ablation by combination of cavitation & thermal processes
 - Nd:YAG (1064nm) and diode (830-980nm) lasers have been used
 - can achieve **target temps up to 85°C**
- success depends on precise delivery of laser fiber to target zone with stabilization of probe during energy delivery to compensate for respirations

HIFU

How does HIFU work?

- focused ultrasound waves used to produce heat energy and form area of coagulative necrosis
- surrounding tissue not affected because energy drops sharply outside focal zone
- single transducers used to produce ablative lesion
 - energy focused by concave transducer or having transducer with acoustic lenses
- smaller focal lengths produce small lesions that do not penetrate deeply ... but lesions are better defined
- can monitor lesion real-time
- **incomplete ablation common in kidney** due to several reasons:
 - respirations make targeting difficult
 - acoustic complexity of heterogeneous tumour and different interphases (rib, wall)

RADIOSURGERY

How does radiosurgery work?

- spherical field of radiation delivered to target lesion
- sharp fall-off curve with minimal exposure to surrounding tissue
- no real-time monitoring possible
- 2 different methods available:
 - 1) interstitial photon radiation } tube inserted into target lesion and radiation delivered via miniature linear accelerator
 - 2) cyberknife } target localized and conformal radiation dose delivered by focusing a multitude of radiation beams at target, yet directing individual beams along different pathways to decrease collateral damage

Chapter #53 – The Adrenals

ANATOMY, HISTOLOGY, AND EMBRYOLOGY

What does the adrenal gland look like on gross pathology?

- sits w/in perinephric fat on anterosuperior and medial aspect of kidney } **within Gerota's**
- 5cm x 3cm x 1cm and yellow-gold in colour
- weighs ~5g } 5-10g at birth → cortex plays a large role in embryogenesis and homeostasis
→ susceptible to hemorrhage at birth as it atrophies
- rich blood supply → inferior phrenic, aorta, renal } **inferior phrenic is MAIN supply**
→ 6-7 mL/g per minute
→ enters circumferentially } anterior & posterior surfaces are avascular
- venous drainage differs → into IVC on R (usually slightly post.) } 5-10% have accessory veins into
R renal vein, R hepatic vein, etc
→ into left renal vein on L (**also has left inferior phrenic vein**)

What is the embryologic origin of the adrenal gland?

- **cortex → from mesoderm**
- **medulla → from neuroectoderm**

What is the histologic appearance of the adrenal gland?

- adrenal cortex is 90% of the gland → zona glomerulosa → mineralocorticoids (aldosterone)
→ zona fasciculata \ glucocorticoids (cortisol),
→ zona reticularis / androgens, and estrogens
- zonation of adrenal cortex is complete by 18 months, and reaches adult configuration at 10 yrs
- adrenal medulla is from neural crest cells → soft & jelly-like (can be dissected free of cortex)
→ composed of mainly chromaffin cells that are richly
innervated by preganglionic sympathetics
→ catecholamines (Epi, some NE and dopamine)
- primitive medulla developed by wk 20, but distinct medulla not present until atrophy of fetal cortex

What is the innervation of the adrenal gland?

- **only medulla is innervated**
- T10 to L1 sympathetics } release of EPI and NE

What is the lymphatic drainage of the adrenal gland?

- lateral aortic LN chain that extends from diaphragm to ipsilateral renal artery

ADRENAL PHYSIOLOGY

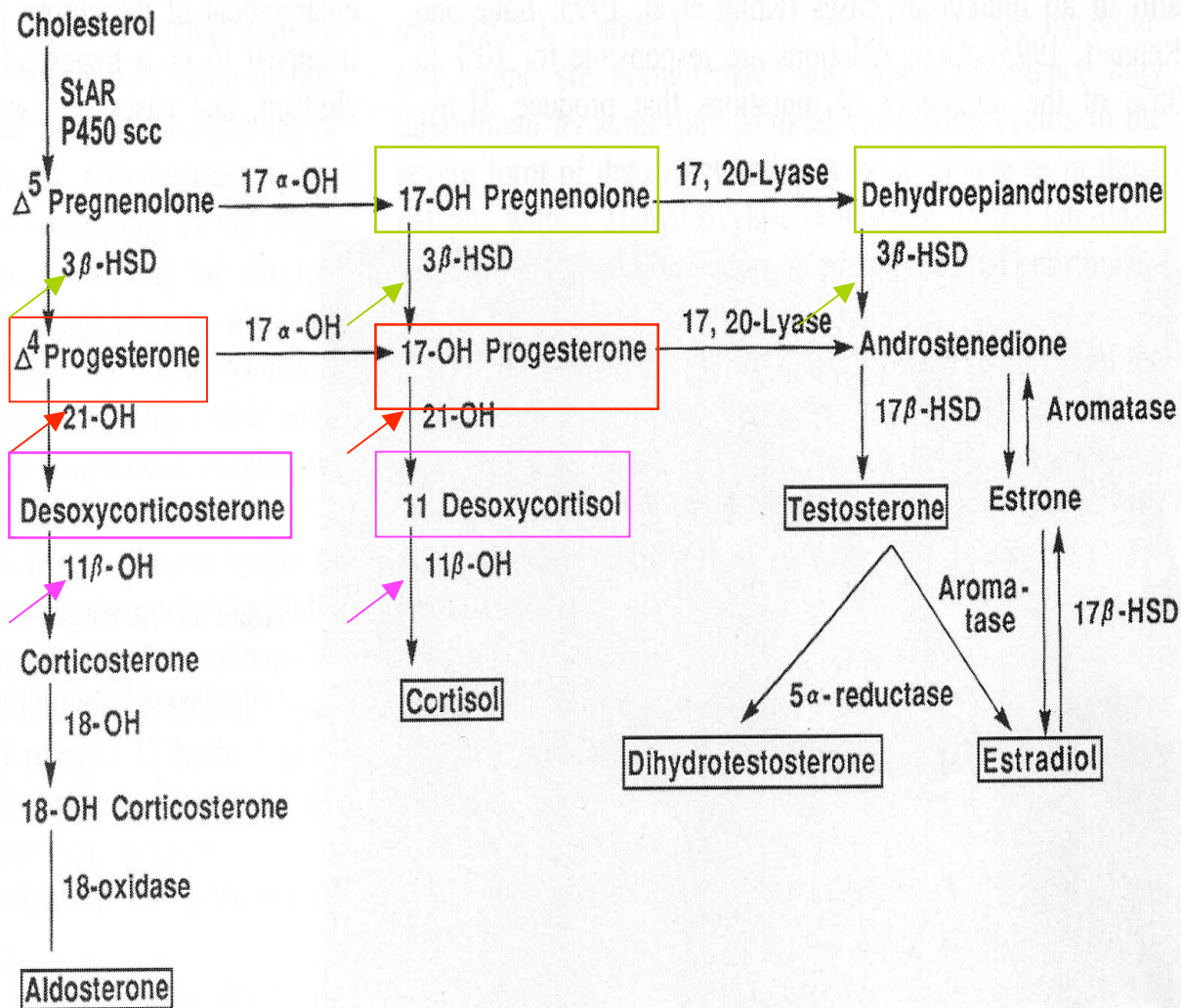
Adrenal Cortex

Which steroid hormones are produced in the adrenal cortex?

- zona glomerulosa → aldosterone
- zona fasciculata & reticularis → cortisol
 - DHEA & DHEAS (most is converted peripherally)
 - androstenedione, testosterone

What is the rate limiting step in the formation of these hormones?

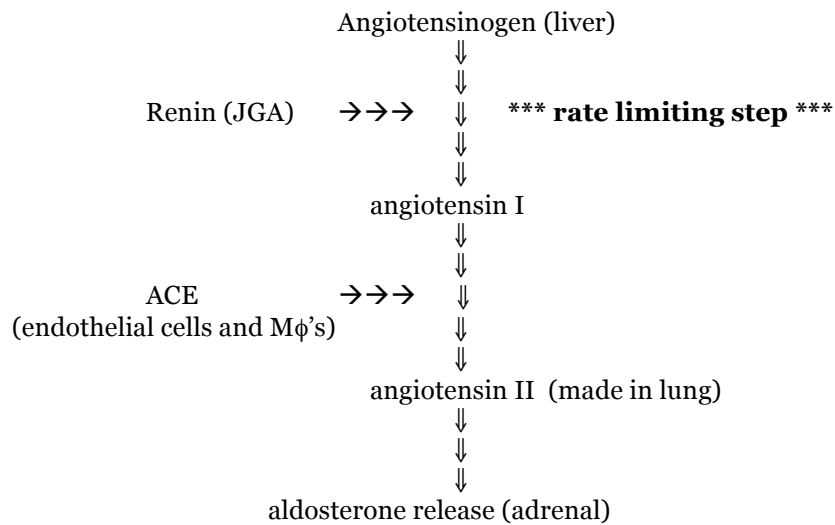
→ conversion of cholesterol to pregnenolone } StAR/P450 pathway



How do the steroid hormones exert their effects?

- **diffuse passively into cells then bind and activate receptor proteins**
- activated receptor-ligand complex then binds to specific DNA sequences, activating gene transcription
 - **sex hormone receptors are mostly in nucleus**
 - **cortisol hormone receptors are mostly in cytoplasm**

Describe the Renin-Angiotensin-Aldosterone system.



List 5 endogenous stimulators of renin release } } } “Salty BP BP”

- ↓'d Salt (NaCl) to macula densa (DCT)
- ↓'d Blood volume (JG cell stretch)
- ↓'d Perfusion pressure
- ↑'d β_1 -adrenergic activity
- ↑'d PGs

List inhibitors of renin release

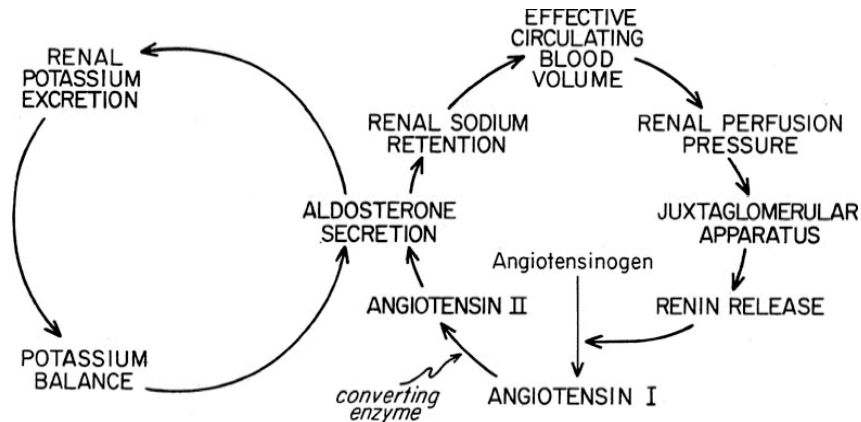
- ↑'d macula densa NaCl
- ↑'d perfusion pressure
- β -blockers
- ↑'d cellular Ca^{++}
- AT II
- ADH
- ANP

What are the effects of AT II?

- 1) kidney → **EFFERENT arteriolar vasoconstriction } to maintain GFR**
 - ↓'s renin secretion (negative feedback)
 - **tubular water & Na reabsorption** } at high []'s, inhibits Na reabsorption in PCT
 - mesangial cell contraction to decrease glomerular filtration coefficient
 - ↓'s **medullary blood flow** resulting in concentration of urine
 - **plays a role in fetal renal development**
- 2) vascular → peripheral vasoconstriction (kidney, skin, mesentery, coronaries, brain)
- 3) adrenal → stimulates **aldosterone secretion** } Na reabsorption
- 4) CNS → **increased BP, thirst, and salt appetite**
 - increased secretion of corticotropin, prolactin, oxytocin, vasopressin
- 5) gonads → role not clear

What regulates the release of aldosterone?

- 1) **primarily AT II** (made in lung due to conversion by ACE) } renal perfusion RAAS
- 2) ACTH is secondary
- 3) K⁺



What are the effects of aldosterone?

- active in kidney, gut, salivary glands, and sweat glands
- Na and K balance
- 1) Na reabsorption
- 2) K secretion
- 3) stimulates ADH secretion (posterior pituitary)

How is aldosterone metabolized?

- poorly bound to albumin and plasma protein
- **short T_{1/2} → 20-30 minutes**
- metabolized in liver, excreted by kidneys

What regulates the release of cortisol?

- **primarily ACTH**
- involves hypothalamus, pituitary, and adrenal → diurnal variation (highest in AM)
- CRH (hypothalamus) → POMC (ant pituitary) → ACTH (ant pituitary) → cortisol (adrenals)

What regulates the release of ACTH?

- increased synthesis
 - CRH
 - vasopressin
 - epinephrine
 - negative feedback
 - cortisol
- | | |
|-----------------------------|-------------|
| → AT II | → oxytocin |
| → ANP | → VIP |
| → gastrin-releasing peptide | → serotonin |

What other proteins are derived from POMC, the precursor to ACTH?

- | | |
|------------------------------------|-------------------------|
| - β-lipotrophin | - β-endorphin |
| - α-melanocyte stimulating hormone | - methionine enkephalin |
| - β-melanocyte stimulating hormone | |

How is cortisol metabolized?

- 80% bound to corticosteroid binding globulin
- 10-15% bound to albumin
- **7-10% free → metabolically active**
- metabolized by the liver

What can cause elevated urine cortisol levels?

- Cushing's
- 3% of lean or obese patients
- 3% of critically ill patients

What are the effects of cortisol?

Table 53-1 -- Effects and Implications of Glucocorticoids

<i>Effects</i>	<i>Clinical Implications</i>
Enhance skeletal and cardiac muscle contraction	Absence results in weakness
Cause protein catabolism	Excess results in wastage and weakness
Inhibit bone formation	Excess decreases bone mass
Inhibit collagen synthesis	Excess causes thin skin and fragile capillaries
Increase vascular contractility and decrease permeability	Absence makes it difficult to maintain blood pressure
Have anti-inflammatory activity	Exogenous steroid is useful in treating inflammatory diseases
Have anti-immune system activity	Exogenous steroids are useful in treating transplantation and various immune diseases
Maintain normal glomerular filtration	Absence reduces glomerular filtration

What regulates the release of adrenal androgens?

- **primarily ACTH } not by gonadotropins**
- sometimes independent of ACTH
 - stress → adrenarche
 - aging → fasting
 - puberty

What are the effects of adrenal androgens?

- weakly active } only relevant in pathologic states (eg CAH)

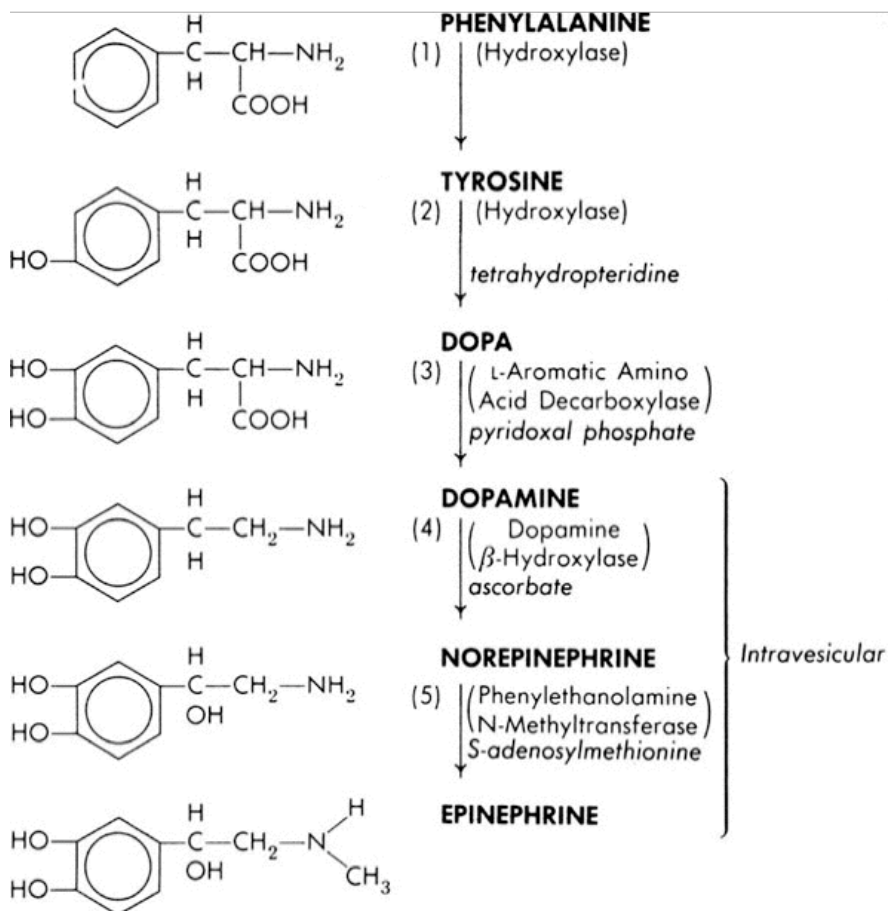
How are adrenal androgens metabolized?

- DHEA is converted to DHEAS in periphery
- **elevated DHEA, androstenedione, or 17-ketosteroids out of proportion to cortisol production makes one suspicious of adrenal carcinoma**
- elevated DHEA & testosterone are the hallmarks of adrenal tumours in women presenting w/ hirsutism

Adrenal Medulla

Which catecholamines are produced in the adrenal medulla?

- **primarily epinephrine (converted from NE)**
- also some NE and dopamine } **NE is most common catecholamine made in neurons**
- **enzyme PNMT** catalyzes methylation of NE to epi → only found in adrenal medulla



How are catecholamines synthesized?

- synthesis occurs in the adrenal gland, CNS, and adrenergic nerve terminals
- **precursors are phenylalanine & tyrosine } made in chromaffin cells**
- **in adrenal, EPI is main catecholamine produced (converted from NE by enzyme PNMT)**
 - **NE is main catecholamine produced in sympathetic neurons**
 - overall, NE accounts for ~73% of catecholamines in plasma } 14% Epi

} 13% dopamine
 - **Pheochromocytomas have mostly NE**

What stimulates catecholamine release from the adrenal medulla?

→ released from vesicles

- stress
- pain
- hypoTN
- Na depletion
- cold/heat
- hypoglycemia
- asphyxia

What are the effects of catecholamines?

→ they exert varied effects by stimulating different receptors (adrenoreceptors)

Alpha-Adrenergic

Alpha₁

Postsynaptic agonists

Vascular smooth muscle—vasoconstriction

Prostate—contraction

Liver—glycogenesis

Alpha₂

Presynaptic—inhibit norepinephrine release

Postsynaptic—agonist

Large veins—venoconstrictor

Brain—decrease sympathetic outflow

Pancreas—inhibit insulin secretion

Gut—relaxation

Adipocyte—inhibit lipolysis

Beta-Adrenergic

Beta₁

Heart—inotropic and chronotropic effect

Adipocyte—lipolysis

Kidney—stimulate renin release

Beta₂

Lung—bronchodilatation

Vascular smooth muscle—vasodilatation

Liver—gluconeogenesis

Uterus—relaxation

Gut—relaxation

Dopaminergic

DA₁: Vascular—vasodilatation

DA₂: Presynaptic—inhibit norepinephrine release

How are catecholamines metabolized?

- **short T_{1/2} of 20 seconds**
- degraded by COMT or MAO enzymes
- metabolites excreted by kidneys

What are the metabolites of catecholamines in urine?

- **VMA (primary metabolite)**
- metanephrines
- normetanephrines

What is the best test for pheochromocytoma?

- **serum metanephrines → most sensitive and specific (NOT AVAILABLE IN CANADA)**

CUSHING'S SYNDROME

What is Cushing's syndrome?

- **syndrome caused by excess circulating glucocorticoids**
- presents in young adults and more common in F
- rare (2-3 per million)
- entity called "subclinical Cushing's" exists and is more common
 - 3-5% of patients with "metabolic syndrome"
 - 24% of patients with adrenal incidentalomas

What are the causes of Cushing's syndrome (CHART)?

- 1) **ACTH-dependent (↑ ACTH)**
 - **Cushing's disease (pituitary adenoma) } most common - 70%**
 - ectopic ACTH } 10% (atypical presentation)
 - ectopic CRH } <1%
- 2) **ACTH-independent (↓ ACTH)**
 - **exogenous steroids } MOST COMMON CAUSE OVERALL**
 - adrenal adenoma } 10%
 - adrenal carcinoma } 8% → much more common cause in kids though
 - micronodular adrenal hyperplasia } 1%
 - macronodular adrenal hyperplasia } <1%
- 3) pseudo-Cushing's
 - major depressive d/o } <1%
 - chronic EtOH } <1%

What are the sources of ectopic ACTH (CHART)?

- "LP The BP" (in order)
- 1) **Lung Ca (52%)**
 - 2) **Pancreatic Ca (11%)**
 - 3) **Thymoma (11%)**
 - 4) **benign Bronchial adenoma (5%)**
 - 5) **Pheo (3%)**
 - 6) **Ca of thyroid, liver, prostate, ovary (2% each)**
 - 7) **mediastinal, breast, parotid, esophageal Ca**
 - 8) **paraganglioma, ganglioma**

What clinical features of Cushing's syndrome are suggestive of a functional adrenal carcinoma?

- 1) virilization w/ cortisol excess (adults only)
- 2) hirsutism
- 3) elevated 17-ketosteroids + DHEAS levels

What are the goals of management of Cushing's syndrome?

- 1) lower daily cortisol secretion to normal levels
 - 2) eradication of any tumour threatening health
 - 3) leave patient with no permanent endocrine deficiency
 - 4) avoidance of permanent dependence on meds
- also need to r/o pseudo-Cushing's

What are the clinical manifestations of Cushing's syndrome?

Table 53-5 -- Clinical Manifestations of Cushing's Syndrome

Manifestation	All (%) *	Disease (%) [†]	Adenoma or Carcinoma (%) [‡]
Obesity	90	91	93
Hypertension	80	63	93
Diabetes	80	32	79
Centripetal obesity	80	—	—
Weakness	80	25	82
Muscle atrophy	70	34	—
Hirsutism	70	59	79
Menstrual abnormalities, sexual dysfunction	70	46	75
Purple striae	70	46	36
Moon facies	60	—	—
Osteoporosis	50	29	54
Early bruising	50	54	57
Acne, pigmentation	50	32	—
Mental changes	50	47	57
Edema	50	15	—
Headache	40	21	46
Poor healing	40	—	—

From Scott HW Jr: *Surgery of the Adrenal Glands*. Philadelphia, JB Lippincott, 1990.

*** patients with ectopic ACTH do not present with the typical features ***

→ instead get cachexia, HTN, hypoK alkalosis & skin pigmentation

*** kids get weight gain & growth retardation ***

*** virilization in F or feminization in M should raise the question of adrenal carcinoma ***

Who should be screened for Cushing's syndrome (CHART)?

1) signs and symptoms

- central obesity with:
- 1) facial rounding + plethora
 - 2) increased supraclavicular & dorsocervical fat
 - 3) cutaneous wasting + ecchymoses
 - 4) wide violaceous striae (>1cm)
 - 5) proximal myopathy
 - 6) increased lanugo hair
 - 7) superficial fungal infections
 - 8) growth retardation (in kids)

2) clinical diagnosis

→ metabolic syndrome X

- 1) DM (Hgb A1c >8%)
- 2) HTN
- 3) hyperlipidemia
- 4) PCOS

→ hypogonadotropic hypogonadism

- 1) oligomenorrhea, amenorrhea, infertility
- 2) decreased libido and impotence

→ osteoporosis (esp with rib fracture)

- 1) <65 yrs

→ incidental adrenal mass

Laboratory Diagnosis

How do you diagnose Cushing's syndrome?

→ **DEMONSTRATION OF CORTISOL HYPERSECRETION is KEY**

- 1) **24hr urine free cortisol** → also order 24 urine creatinine to assess adequacy of specimen
 - **Cushing's if >3x upper limit of normal (>100mg/24hr)**
 - ideally should have 2 or 3 consecutive 24hr specimens
 - **MOST DIRECT AND RELIABLE INDEX OF CORTISOL**
 - can also add am/pm plasma cortisol } **loss of diurnal variation in Cushing's syndrome**
- 2) **1mg dexamethasone suppression test** → **reserved for equivocal 24hr urine free cortisol**
 - **some use it as 1st line test**
 - dexamethasone given night before at 11pm
 - measure plasma cortisol next morning
 - **Cushing's if cortisol still elevated (>138 nmol/L)**
 - less reliable in obese patients so do the 2 day test, which involves 0.5mg po q6h for 2days prior
- 3) late-night salivary cortisol [] measurement → new test used by endocrinologists

How do you differentiate between ACTH-dependent from ACTH-independent Cushing's?

- 1) **serum ACTH + cortisol** → ideally measured at 2am, when both are lowest
 - commonly measured in late afternoon
 - preferable to have 2 or 3 measurements on separate days
 - **if ACTH is high (>50pg/mL), then it's ACTH-dependent**
 - ie Cushing's disease, ectopic ACTH or CRH syndrome
 - **if ACTH low (<5 pg/mL), then it's ACTH-independent**
 - ie exogenous steroids, adrenal adenoma, adrenal Ca, hyperplasia
- 2) **high dose 8mg DST** → **pituitary disease if >50% decrease in cortisol**
 - **adrenal Cushing's if only relative resistance to DST** } mild ↓ in cortisol
 - ectopic ACTH if complete resistance to DST (no change in cortisol level)

How do you differentiate between the types of ACTH-dependent Cushing's syndrome?

→ eg Cushing's disease VS ectopic ACTH

- 1) **metyrapone stimulation test** → blocks conversion of 11-desoxycortisol to cortisol, causing ↑'d ACTH from pituitary due to low cortisol levels, and so urine 17- hydroxycorticosteroid also ↑'s
 - tests for pituitary insufficiency
 - **Cushing's disease if ↑'d urinary 17-OH-corticosteroid**
 - **ectopic ACTH if little or no increase in ACTH & urinary 17-OH-corticosteroid (due to suppressed pituitary)**
- 2) petrosal venous sinus sampling → most direct way to demonstrate Cushing's disease
 - compare petrosal venous sinus ACTH to peripheral ACTH
 - invasive with significant complications reported
- 3) Imaging → CT, MRI, or radionuclide imaging for somatostatin receptors
 - can identify occult ACTH-secreting tumours

Radiographic Localization

What imaging modalities are used to assess adrenal pathology?

- **CT is first line**
- MRI +/- gadolinium enhancement } **MRI better for pheo**

What are the CT findings suggestive of adrenal hyperplasia?

- 1) diffuse thickening and elongation of adrenal rami
- 2) sometimes see prominent glands bilaterally (can be called normal)
- 3) **multinodularity of both adrenals (nodules <2cm)**

List radiologic features suggestive of adrenal ADENOMA

- 1) usually 2-5cm
→ large adenomas can look like carcinomas on CT
- 2) solitary
- 3) smooth contour, sharp margins, homogeneous
- 4) atrophy of contralateral gland
- 5) **low CT density due to high concentration of lipid (<10 HU)**
- 6) **early CT washout >60% } DIAGNOSTIC**
- 7) **loss of signal on “out of phase” T1 MRI**
- 8) **low signal intensity on T2 MRI**

List radiologic features suggestive of adrenal CARCINOMA

- 1) **size >5cm**
- 2) irregular, poorly defined border + thick enhancing rim
- 3) invasion of adjacent structures
- 4) heterogeneous attenuation with **necrosis & calcification (more common but not diagnostic)**
- 5) **CT enhancement >10 HU**
- 6) **slow CT contrast washout**
- 7) **no signal drop out on “out of phase” T1 MRI**
- 8) **high signal density on T2 MRI**



→ CT OF ADRENAL CARCINOMA

What are the MRI findings suggestive of adrenal carcinoma?

- usually only needed in Cushing's patients if carcinoma is suspected
- 1) higher signal intensity than that in spleen → **bright on T2**
→ adenomas are not bright
 - 2) **no signal drop out on “out of phase” T1 MRI**

Treatment

What is the treatment of Cushing's disease?

- 1) **trans-sphenoidal hypophyseal Sx** → **initial treatment of choice** } 85-95% cure rate
→ low complications, rare recurrences
→ may get transient diabetes insipidus or decrease in cortisol levels needing replacement
- 2) pituitary RADs → reserved for patients with unsuccessful trans-sphenoidal surgery
→ ~80% remission rates after unsuccessful trans-sphenoidal surgery
- 3) bilateral adrenalectomy → need cortisol replacement
→ **10-20% develop Nelson's syndrome**
- 4) meds → can be used for specific hormone-secreting pituitary adenomas

What is Nelson's syndrome?

- **pituitary tumours (usually chromophobe adenoma)** after B/L adrenalectomy
→ **H/A, visual disturbances, deep pigmentation**
 - perhaps due to lack of HP axis feedback and high levels of ACTH and related compounds
 - may arise many years after bilateral adrenalectomy
 - patients need f/u with ACTH levels and evaluation of the sella turcica
- Rx → can be prevented by prophylactic pituitary RADs

What is the treatment of ectopic ACTH syndrome?

- 1) treat primary tumour/source of ectopic ACTH
→ lung Ca, pancreatic Ca, thymoma, benign bronchogenic adenoma, pheo, etc
- 2) meds to decrease functional steroids
 - aminoglutethimide → blocks conversion of cholesterol to pregnenolone (StAR, P450)
→ watch for adrenal insufficiency b/c aldosterone production also impaired
 - metyrapone → blocks conversion of 11-desoxycortisol to cortisone (11 β -hydroxylase)
→ doesn't result in salt wasting at the normal doses
 - ketoconazole → blocks CYP450-mediated steps of steroid synthesis
 - mifepristone → cortisol receptor blocker
 - mitotane

How common are adrenal tumours that produce Cushing's syndrome during pregnancy?

→ **rare because disease causes irregular menstruation**

- 33% are ACTH-dependent \ opposite in non-pregnant cases, where
- 60% are ACTH-independent / ACTH-dependent cause is more common

What happens during normal pregnancy?

- normal diurnal variation of cortisol
- elevated plasma cortisol-binding protein
- elevated plasma protein bound & unbound cortisone levels
- slight rise in urinary free cortisol levels
- some resistance to DST that progresses w/ each trimester → not total absence of suppression
→ still can be used to Dx Cushing's

What is the treatment of Cushing's syndrome in pregnant patient?

→ **maternal & fetal morbidity reduced with treatment**

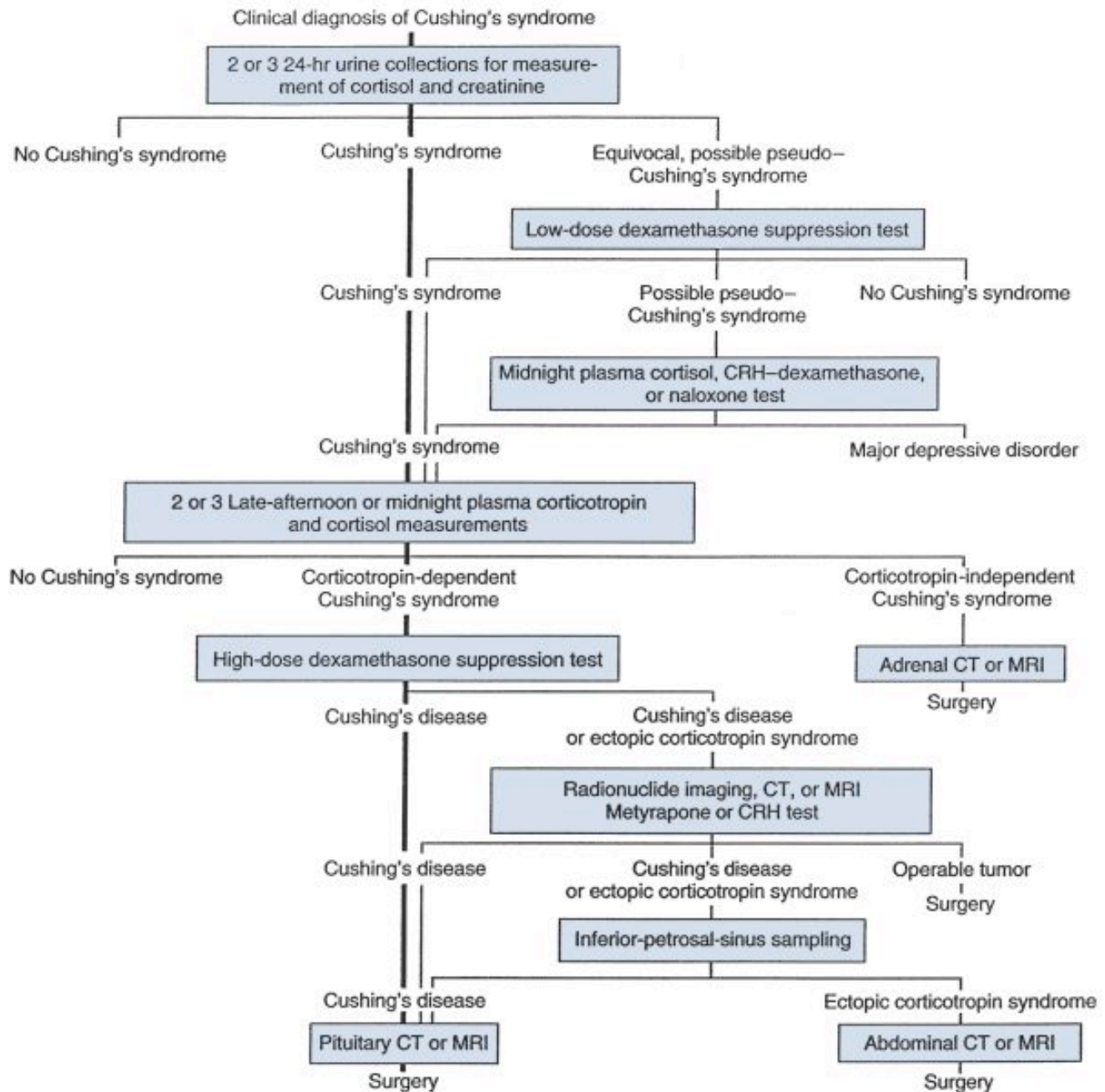
- can surgically remove adenoma during pregnancy → wait until T2
- can use meds → metyrapone

What side effects of Cushing's is passed on to the fetus?

- minimal } maternal cortisol doesn't transfer across placenta very much
- } **fetus doesn't need steroid replacement after birth**
- } does cause **higher rates of prematurity**

What is the treatment for a functional adrenal adenoma causing Cushing's syndrome?
→ surgical removal

*** see Chapt #54***



ADRENAL CARCINOMA

What is the epidemiology of adrenal carcinoma?

- rare disease → 1 in 1.7 million
- poor overall survival → 16-37% despite Rx
→ **40% present with mets already**
- **most are sporadic & unilateral** → unknown etiology

What hereditary diseases are associated with bilateral adrenal carcinomas? }} “CL1MB”

→ accounts for only 2-6% of all adrenal tumours

- 1) **Carney complex**
 - AD multiple neoplasia syndrome (mainly in kids)
 - spotty skin pigmentation, myxomas (cardiac, skin), endocrine tumours (adrenal, Sertoli cell)
- 2) **Li-Fraumeni syndrome**
 - AD disorder that is characterized by multiple different cancers
 - breast, brain, leukemia, sarcomas, etc
 - due to p53 tumour suppressor gene mutation
- 3) **MEN type I**
 - AD disorder (11q13)
 - PTH tumours + pituitary adenomas + pancreatic islet cell tumours
- 4) **Beckwith-Wiedemann syndrome**
 - rare overgrowth syndrome
 - omphalocele, macroglossia, macrosomia, organomegaly, Wilms' tumours

What is the classification of primary adrenal carcinomas (CHART)?

1) functional → 60%

- **Cushing's syndrome (39.5%)**
- Cushing's + virilization (24%)
- Virilization alone of females (20%) → mainly in kids
- feminization of males (6%)
- hyperaldosteronism (2.5%)

*** most tumours secrete multiple compounds ***

2) non-functional → 40%

- may have worse prognosis
- may become functional

List the 9 histologic features of the Weiss Criteria that predicts adrenal carcinoma (CHART)

→ sometimes, it may be difficult to discern large adenoma from carcinoma

→ lesion considered malignant if **≥3** are present

- 1) high mitotic rate (>5 per 50 hpf)
- 2) atypical mitoses
- 3) venous invasion
- 4) high nuclear grade (Fuhrman 3-4)
- 5) absence of cells with clear cytoplasm (<25% of cells)
- 6) a diffuse growth pattern (more than 1/3 of tumour)
- 7) necrosis
- 8) sinusoidal invasion
- 9) capsular invasion

Functional Tumours

What features in Cushing's syndrome are suspicious for a functional adrenal carcinoma?

- 1) virilization with cortisol excess is hallmark of Cushing's from functional adrenal carcinoma
→ except in kids
- 2) hirsutism (more common with carcinoma)
- 3) elevated levels of 17-ketosteroid + DHEAS + cortisol (more common with carcinoma)
→ POOR PROGNOSIS

What is the risk of adrenal carcinoma in TESTOSTERONE-secreting lesions of the adrenal?

→ **not common**

- **virilization without elevated urinary 17-ketosteroids suggests benign lesions**
 - ovarian or adrenal } usually ovarian not adrenal
 - **virilization + elevated urinary 17-ketosteroids is classic Cushing's secondary to functional adrenal carcinoma**
- usually small (<6cm)
- usually benign → 8/47 were malignant in Mattox and Phelan '87
- even when malignant, better prognosis

What is the risk of adrenal carcinoma in ESTROGEN-secreting lesions of the adrenal?

→ **very common**

- presents with gynecomastia, testicular atrophy, ED, decreased libido
- tumours secrete androstenedione → converted peripherally to estrogen
- usually large
- usually **highly malignant** → **80%**
→ 3yr survival is <20%
- wide excision is only Rx → no effective adjunctive Rx available

What is the risk of adrenal carcinoma in ALDOSTERONE-secreting lesions of the adrenal?

→ **very rare**

- primary hyperaldosteronism usually due to small, benign, solitary adenoma, Conn's syndrome, or bilateral adrenal hyperplasia
- if from adrenal carcinoma, usually have hyperaldosteronism + abN cortisol/androgen secretion
 - usually >3cm in size (benign adenomas are rarely >3cm)
 - poor prognosis
 - wide excision is only Rx → no effective adjunctive Rx available

Adrenal Carcinoma in Kids

How common are adrenal carcinomas in kids?

- not common → 6% of malignant adrenal tumours
→ majority of malignant adrenal tumours are neuroblastomas
- survival is better than adults → double the survival rate
- still lethal and no adjunctive Rx
- most are hormonally active → ?earlier detection
→ **unlike adults, Cushing's in kids is more commonly due to carcinoma (not adenoma)**
→ virilization in girls
→ precocious puberty in boys

What paediatric syndromes are associated with adrenal carcinomas?

- Beckwith-Wiedemann syndrome
- isolated hemihypertrophy
- Li-Fraumeni syndrome

Management of Adrenal Carcinoma

What is the prognosis of adrenal carcinoma?

- **highly malignant tumour } except in testosterone-secreting tumours (which are rare)**
- local and hematogenous spread } 40% present with mets
- overall, 5yr survival of 20-35%

What are the most common sites of metastasis of adrenal carcinoma?

- 1) lung
- 2) liver
- 3) LN
- 4) bone

List radiologic features suggestive of adrenal CARCINOMA

- 1) **size >5cm**
- 2) irregular, poorly defined border + thick enhancing rim
- 3) invasion of adjacent structures
- 4) heterogeneous attenuation with **necrosis & calcification (more common but not diagnostic)**
- 5) **CT enhancement >10 HU**
- 6) **slow CT contrast washout**
- 7) **heterogeneous with no signal drop out on “out of phase” T1 MRI**
- 8) **high signal density on T2 MRI**
- 9) venous invasion on MRI

What is the management of adrenal carcinoma?

- 1) **surgical resection is prime modality of Rx → wide resection with LNs en bloc**
 - 2) **chemo (cisplatin, etoposide) not very effective → due to MDR P-glycoprotein expression**
 - 3) **RADs not useful → just for palliation**
 - 4) **adrenolytics } DDT derivative**
 - no survival benefit
 - marginal benefit if high-serum levels or given post-op as adjuvant Rx
 - adrenal insufficiency can occur so should measure cortisol & aldo
 - } mitotane
 - } suramin
 - } ketoconazole
 - } metyrapone
 - } aminoglutethimide

used mainly to relieve the devastating symptoms of cortisol or aldosterone excess
 - 5) **transarterial embolization → used to Rx symptoms in a patient with mets**
- *** **new data suggests adjuvant mitotane has survival benefit (Terzolo – NEJM '07)**

What are the poor prognostic RFs for adrenocortical carcinoma?

- high stage & unresectability
- high grade
- large size (very poor if >12cm)
- presence of intratumour hemorrhage
- adult

What are the toxic S/E's of adrenolytics (eg mitotane)?

- GI
- neuro
- dermatologic disorders
- most go away with cessation of Rx

Outline the staging of adrenal tumours.

T1	< 5 cm, localized to adrenal
T2	≥ 5 cm, localized to adrenal
T3	Local invasion, no adjacent organ
T4	Adjacent organ invasion
N1	Regional nodes
M1	Distant mets
Stage I	T1NoMo
Stage II	T2NoMo
Stage III	T3 or N1
Stage IV	T4, T3N1Mx, or M1

ADRENAL METASTASES

What are the imaging findings suggestive of adrenal mets?

- 1) enhancement on CT
 - 2) no contrast washout on CT
 - 3) high intensity on T2 MRI
 - 4) +ve on PET scan
- also –ve on NP-50 scintigraphy (adenoma takes it up)

What are the most common primaries that mets to the adrenal? }} “Major League Baseball RCC”

→ adrenal mets more common than primary adrenal malignancies

→ 75% of adrenal lesions in cancer patients are adrenal mets

- | | |
|--|------------------------------------|
| 1) Melanoma → 50% of patients | \ } FNA Bx after you r/o PHEO
/ |
| 2) Lung Ca → 50% | |
| 3) Breast Ca → 50% | |
| 4) RCC → 40% | |
| 5) contralateral adrenal carcinoma | |
| 6) bladder | |
| 7) colon | |
| 8) esophagus | |
| 9) GB | |
| 10) liver, pancreas, prostate, stomach | |

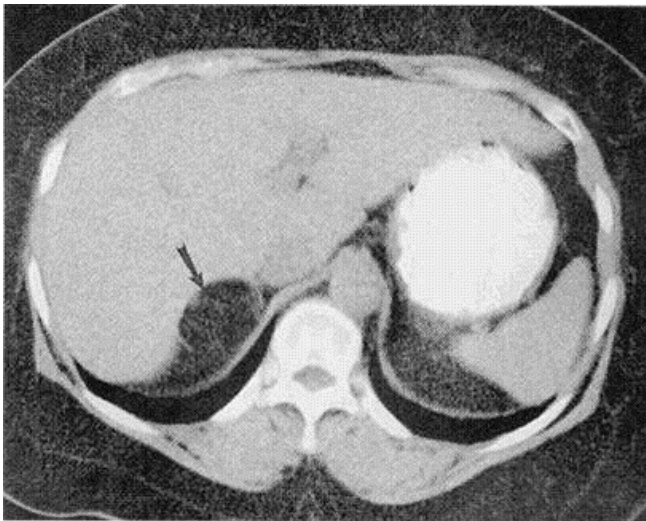
ADRENAL MYEOLIPOMA

What are adrenal myelolipomas?

- **non-functioning, benign lesion** } usually <5cm and unilateral
- contains **hematopoietic & fatty elements**
- more common in M (~2:1) and patients are usually obese
- **pain is the most common presentation**
- classic appearance on CT and MRI → see **fat on imaging (< -30 HU)**
 - no enhancement on CT
 - rarely calcified

What is the management of adrenal myelolipomas?

- **functional tests** to r/o coexisting functional cortical adenoma
 - if non-functional, no further w/u needed
- large lesions may be confused with necrotic adrenal carcinoma
- **remove if pure adrenal lipoma**
 - could be retroperitoneal liposarcoma or adrenal leiomyosarcoma



→ CT OF ADRENAL MYEOLIPOMA

Benign Adenoma

List radiologic features suggestive of adrenal ADENOMA

- 1) usually 2-5cm
 - large adenomas can look like carcinomas on CT
- 2) solitary
- 3) smooth contour, sharp margins, homogeneous
- 4) atrophy of contralateral gland
- 5) **low CT density due to high concentration of lipid (<10 HU)**
- 6) **early CT washout >60% } DIAGNOSTIC**
- 7) **loss of signal on "out of phase" T1 MRI**
- 8) **low signal intensity on T2 MRI**

ADRENAL ONCOCYTOMA

What is an adrenal oncocytoma?

- rare, benign neoplasm } **non-functional**
 - composed of epithelial cells with abundant acidophilic granular cytoplasm
 - often large before detection
 - difficult to distinguish from adrenal carcinoma
- Rx → surgical

ADRENAL CYSTS

List some of the different types of adrenal cysts

- 1) **endothelial** (or lymphangiomatous) → **45%**
- 2) **pseudocysts** (eg post-hemorrhage) → **40%**
- 3) epithelial (true) → 9%
- 4) parasitic (echinococcal disease) → 7%
- 5) cystic malignancy } neuroblastoma, adrenal corticocarcinoma, mets
- 6) cystic pheo
- 7) abscess

What is the significance of adrenal cysts?

- usually incidental finding
 - mostly unilateral
 - 15% have calcifications → doesn't mean malignant
- Rx → perc drain if symptomatic
→ lap decortication if recurrent and symptomatic

ADRENAL INSUFFICIENCY

What is Addison's disease?

- **chronic adrenal insufficiency**
- rare disease → 3 per million
- 10-30% also have other endocrine disorders
 - hyperT4 or hypoT4 (17%)
 - DM (12%)
 - gonadal dysfunction (12%)

What are the causes of adrenal insufficiency/Addison's disease?

- **"MASH Adrenal(ytics) FAST"**
- **Malignant infiltration/mets**
 - **Autoimmune destruction (now most common cause)**
 - adrenal autoAb's to 21-hydroxylase } ? part of autoimmune polyendocrine syndrome
 - **Steroid withdrawal (acute)**
 - **Hemorrhage from sepsis** } Waterhouse–Friderichsen syndrome
 - **Adrenolytics** } aminoglutethimide, ketoconazole, mitotane, suramin, etc
 - **Fungal infections** } histoplasmosis, North and South American blastomycosis, coccidioidomycosis
 - **Atrophy** } process of lymphocytic adenitis with fibrosis
 - **Sarcoidosis**
 - **TB (used to be most common cause)**

How do you diagnose Addison's disease?

- 1) **ACTH infusion → cosyntropin test (0.25mg iv)**
 - measure cortisol levels before and 60min after infusion
 - **failure to see rise of plasma or urine corticosteroid level into N range after ACTH infusion**
- 2) CRH test → 100 µg of human CRH

What are the signs and symptoms of Addison's disease & adrenal insufficiency?

Table 53-10 -- Signs and Symptoms of Chronic Addison's Disease and Acute Adrenal Insufficiency

Prevalence		
Number	%	Symptom
<i>Addison's Disease</i>		
435/462	94	Weakness, tiredness, fatigue
393/438	90	Weight loss
303/351	86	Anorexia
178/268	66	Nausea, vomiting
100/164	61	Unspecified gastrointestinal complaints
35/127	28	Abdominal pain
44/246	18	Diarrhea
15/94	16	Muscle pain
24/168	14	Salt craving
24/166	14	Orthostatic hypotension, dizziness, or syncope
4/33	12	Lethargy, disorientation
<i>Acute Adrenal Insufficiency</i>		
165/165	100	Severe clinical deterioration
98/140	70	Fever
20/31	64	Nausea, vomiting
21/46	46	Abdominal or flank pain
59/165	36	Hypotension
9/28	32	Abdominal distention
25/101	26	Lethargy, obtundation
55/122	45	Hyponatremia
21/83	25	Hyperkalemia

From May ME, Vaughan ED Jr, Carey RM: Adrenocortical insufficiency—clinical aspects. In Vaughan ED Jr, Carey RM, eds: Adrenal Disorders. New York, Thieme Medical, 1989.

What is the treatment of Addison's disease?

- maintenance of glucocorticoids & supplement mineralocorticoids
- 30mg hydrocortisone + 0.1µg fluorohydrocortisone daily

What are the causes of adrenal insufficiency in cancer patients?

- 1) adrenal mets infiltration
- 2) infiltration with lymphoma
- 3) hemorrhagic necrosis from anticoagulation or sepsis
- 4) impaired steroidogenesis in pts receiving adrenolytics (ketoconazole, aminoglutethimide, mitotane)

What is the classic triad of lab abnormalities seen with chronic adrenal insufficiency?

- seen only in 50-60%
- **hypoNa**
- **hyperK**
- **azotemia**

What are the causes of acute adrenal crisis?

- 1) withdrawal of exogenous steroids
- 2) sepsis
- 3) bilateral adrenal hemorrhage
- 4) post-adrenalectomy state

What is the treatment of acute adrenal crisis?

1) emergency Rx

- 19-gauge iv line
- STAT serum lytes, glucose, cortisol, and ACTH } do not wait for results
- infuse 2-3L of NS as fast as possible } watch for fluid overload
- steroids } dexamethasone (decadron) 4mg iv with bolus
OR hydrocortisone (solucortef) 100mg iv then 100mg q8h
- supportive measures PRN
- mineralocorticoids are unnecessary and ACTH is useless

2) subacute treatment after stabilization

- continue NS infusion at lower rate x 24-48hrs
- search for and Rx, if possible, the cause of adrenal crisis
- perform short ACTH stimulation test to confirm Dx
- taper steroids to maintenance dose over 1-3 days
- start mineralocorticoid replacement (Florinef 0.1mg po od) once NS infusion stopped

Selective Adrenal Insufficiency

What is selective hypoaldosteronism?

- rare } **usually due to hyporeninemia OR functional hypoaldosteronism caused by tubular insensitivity to normal aldo levels**
- often seen as unexplained hyperK after relief of chronic obstruction, especially in association w/ CRF
- can also be due to:
 - primary disturbance of zona glomerulosa
 - endogenous impairment of AT II production
 - aldosterone receptor deficiency

What is selective familial glucocorticoid deficiency?

- almost exclusively in **pediatric population**
- presents with **recurrent hypoglycemia + subsequent seizures**
- usually have normal electrolytes → often have delayed Dx

PRIMARY HYPERALDOSTERONISM (eg CONN'S SYNDROME)

Pathophysiology

What is the syndrome of primary hyperaldosteronism?

- HTN
- **suppressed plasma renin activity (PRA)**
- **high urine & plasma aldosterone**

What are the 4 features of primary hyperaldosteronism that predict favorable response to surgery?

- **most patients with primary hyperaldosteronism can have HTN & metabolic abN'ities cured by unilateral adrenalectomy**
- **when aldosterone production is highly autonomous from renin-angiotensin, these patients are likely to respond well after surgery**
- 1) limited effect on aldosterone production despite maneuvers to change AT II levels
 - increasing AT II (AT II infusion or postural stimulation)
 - decreasing AT II (saline infusion, fludrocortisone administration, ACE inhibition)
- 2) increased levels of aldosterone precursors (eg ratio of 18-hydroxycorticosterone to cortisol)
- 3) elevated levels of "hybrid" steroids (eg urinary cortisol C-18-methyloxygenated metabolites)
- 4) lateralization of aldosterone secretion to one adrenal gland

What is the key feature of secondary hyperaldosteronism?

- excess production of renin and AT II results in oversecretion of aldosterone
- **don't see suppression of PRA in response to increased BP and Na load**
- usually caused by renal arterial or parenchymal disease

What is the classic triad for Dx of primary hyperaldosteronism?

- 1) hypoK (after Na repletion)
- 2) suppressed PRA
- 3) high plasma or urine aldosterone (after K supplementation)

List causes of primary hyperaldosteronism

- 1) **aldosterone-producing adenoma (APA)** } **Conn's syndrome** } CURED AFTER Sx
 - **ATII-unresponsive variant (more common)**
 - **ATII-responsive variant**
- 2) **bilateral idiopathic adrenal hyperplasia** } NOT CURED AFTER Sx
- 3) **aldosterone-producing renin-responsive adenomas (AP-RAs)** } CURED AFTER Sx
- 4) **primary adrenal hyperplasia** } CURED AFTER Sx
- 5) **familial forms eg GRA (rare cause)**
- 6) **adrenal carcinoma (rare cause)**

What is Glucocorticoid-remediable aldosteronism (GRA)?

- aka familial hyperaldosteronism type 1 (FH-I) } HF type 2 is not responsive to glucocorticoid Rx
- rare AD disorder } abnormal chromosome 8 (CYP11B1/CYP11B2 gene)
- have strong family hx of HTN, early-onset HTN, and increased risk of intracerebral bleed or aortic dissection
- aldosterone synthesis **regulated by ACTH** not RAAS
- **due to abN synthesis of aldosterone in zona fasciculata** (which usually makes cortisol) instead of zona glomerulosa
- **low PRA but DO NOT HAVE HYPOKALEMIA**
- **HIGH urinary 18-hydroxycortisol and 18-oxocortisol**
- Rx – glucocorticoids (inhibits ACTH and consequently reduces aldosterone production)

What is apparent mineralocorticoid excess type 1?

- HTN + low PRA + low urinary aldosterone + ↑'d urinary metabolites of cortisol rather than cortisone
 - normal cortisol and aldosterone
 - mineralocorticoid receptor usually binds cortisol and aldosterone with equal affinity
 - cortisol level is ~1000fold higher than aldosterone but most of it is inactivated by conversion to cortisone (which has low affinity for mineralocorticoid receptor)
 - **inhibition of 11β-hydroxysteroid dehydrogenase results in ↓'d cortisol to cortisone conversion } higher active cortisol can bind to mineralocorticoid receptor**
- Rx – 1) block either mineralocorticoid receptor (use spironolactone) or renal apical Na channel (use amiloride)
- 2) suppression of endogenous cortisol production (use dexamethasone)
- 3) avoid licorice (glycyrrhizic acid is active ingredient that also inhibits enzyme)

What is Liddle's syndrome?

- rare AD disorder
 - HTN with low PRA + low ATII + hypoK + renal K wasting + low levels of aldosterone
 - deletion mutation results in activation of ENaC (Na reabsorption and K excretion)
→ results in Na-dependent HTN
- Rx – amiloride (must block abN ENaC) } spironolactone doesn't work b/c doesn't act on ENaC

Epidemiology

How common is primary hyperaldosteronism?

- represents 3-30% of HTN'sive patients } classically thought to represent only 1-2% (**controversial**)
- Conn's (APA) was thought to be the most common cause
→ **bilateral adrenal hyperplasia now accounts for a large portion**
- adenoma more likely to be found in younger patients and in women
- adenomas are more common on L
- patients with adenomas usually have more severe symptoms
- patients with adrenal hyperplasia more commonly do not have hypoK

Clinical Characteristics

What are the presenting signs & symptoms of primary hyperaldosteronism?

→ **findings are due to increased total body Na content & deficit in total body K**

- 1) increased Na content
 - HTN
 - NO EDEMA (renal escape phenomenon)
- 2) hypoK
 - nocturia
 - urinary frequency
 - frontal H/A's
 - visual disturbances
 - polydypsia
 - paresthesias/paralysis
 - muscle weakness
 - cramps and tetany
 - mild metabolic alkalosis

What is the mineralocorticoid "renal escape" phenomenon?

- as Na accumulates in body, increased extracellular Na is accompanied by water
 - after a gain of ~1.5kg of excess extracellular fluid, kidneys stop Na reabsorption
 - maintains Na balance
- reason why patients with primary hyperaldosteronism DO NOT HAVE EDEMA

Are patients with primary hyperaldosteronism at increased CV risk?

- possibly yes } equal with either adenoma or hyperplasia
→ **greater risk of A fib, stroke, MI, LV hypertrophy**

What screening tests are used to diagnose primary hyperaldosteronism in patients with HTN?

- ## What measures can be taken to improve diagnostic accuracy of ARR?

- How can you differentiate primary hyperaldosteronism due to adenomas from hyperplasia?

- 1) **postural stimulation test**
 - } in normal individuals, standing stimulates renin & aldosterone
 - } blood test at 8am with pt supine (after sleeping) then again several hrs later after walking around
 - normally aldosterone should increase
 - } there is a **DECREASE IN ALDOSTERONE** seen in patients with
 - a) **ADENOMA** (in more common AT2-unresponsive variant)
 - b) primary adrenal hyperplasia
- 2) cortisol metabolites } 18-hydroxycortisol and 18-oxocortisol **ELEVATED** in patients with primary hyperaldosteronism caused by **ADENOMA**

Lateralizing Tests

Why are lateralizing tests necessary?

- 1) tests to differentiate adenoma from hyperplasia exist but can't identify side
eg postural stimulation test, cortisol metabolites test
- 2) CT and MRI lack sufficient accuracy to identify adenomas <1.5cm
→ incidental, nonfunctioning adrenal masses found in 0.6% of CT scans
→ some patients with adenomas have normal adrenals on CT/MRI

How is adrenal vein sampling performed?

- femoral access
- aldosterone & cortisol levels measured from both adrenal veins and from infrarenal IVC
- infusion of cosyntropin (50µg/hr) used to minimize stress-induced fluctuations
- **valid sample if cortisol level in adrenal vein is at least 2x higher than in IVC**
- **adenoma (APA) = lateralized ratio >5 + serum aldosterone >15ng/dL**

What are the potential complications of adrenal vein sampling?

- difficulty catheterizing short right adrenal vein
- trauma } adrenal hemorrhage can lead to acute adrenal insufficiency
- dilution of blood sampling by blood from nonadrenal source
- episodic change in aldosterone secretion coincident with changes in cortisol

What is the role of radionuclide scintigraphy?

- poor tracer (I^{131} -iodocholesterol NP-59) uptake by tumours <1.5cm } test not routinely used
→ NP-59 concentrates in functional adenomas

Treatment

What is the management of primary hyperaldosteronism due to **bilateral adrenal HYPERPLASIA?**

- **mineralocorticoid receptor antagonist } KEY TO RX**
 - spironolactone is 1st line } 50-300mg/day
 - } S/E's → painful gynecomastia, ED, decreased libido, menstrual irregularities
 - } add amiloride or eplerenone if S/E's
- can do adrenalectomy if evidence of a dominant side

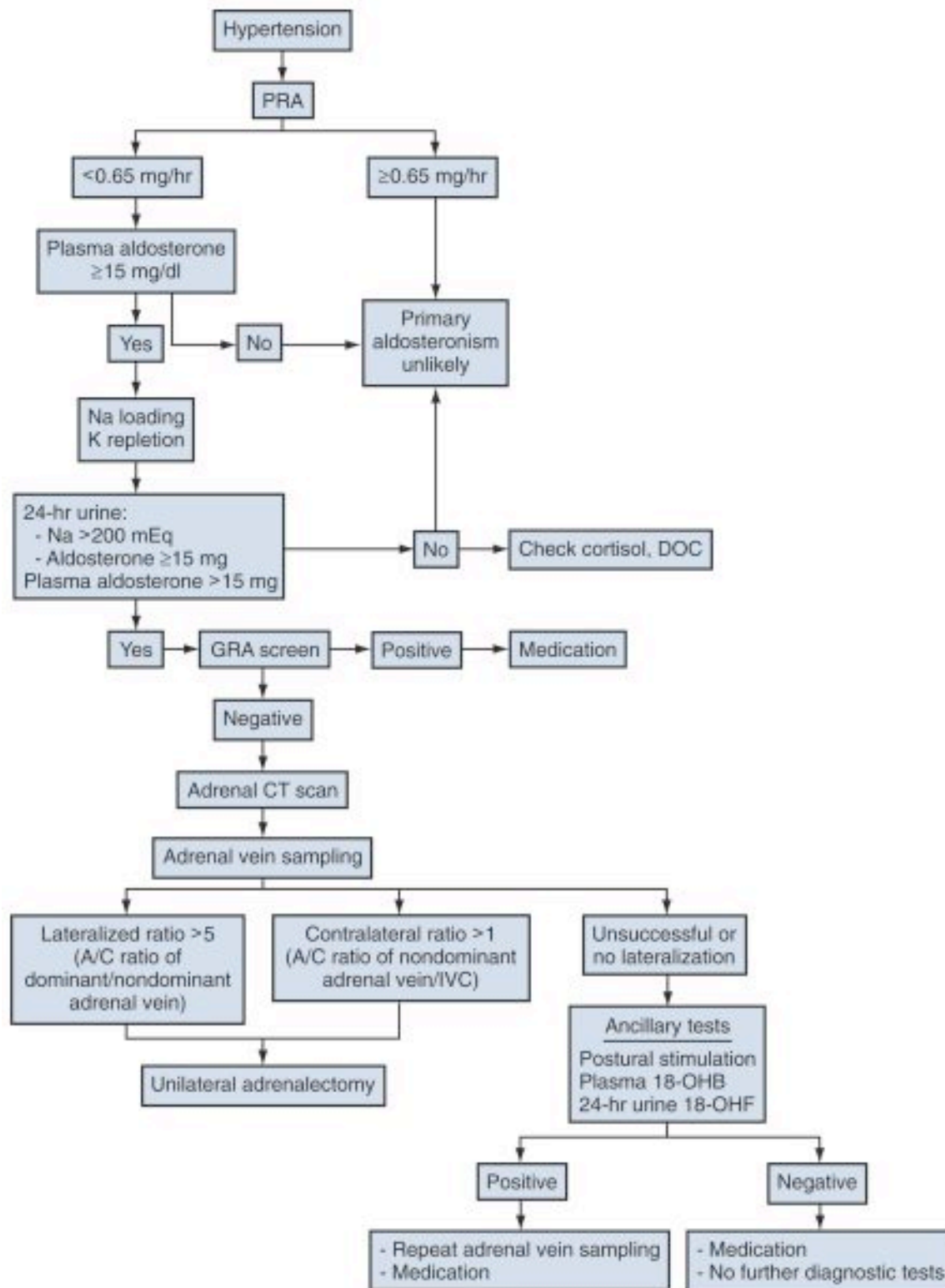
What is the management of primary hyperaldosteronism due to an **aldosterone-producing ADENOMA?**

- usually have +ve postural stimulation test (decrease in aldosterone) or +ve cortisol metabolites to confirm primary hyperaldosteronism is from adenoma (APA)
- **LAP ADRENALECTOMY is STANDARD OF CARE**
 - ~100% have improvement of hypokalemia
 - 90% have good BP control post-op } 40-70% still need anti-HTNsive meds
- all patients with +ve lateralization test had improvement or cure of HTN post-op
- **watch for post-op hypotension and hypoglycemia**

What are the predictors of persistent HTN needing meds post-lap adrenalectomy?

- >50% will still need meds
- age >50
- long duration of HTN
- increased serum creatinine
- pretreatment PRA not very low
- one 1st-degree relative with HTN
- pre-op use of >2 anti-HTNsive meds
- BP controlled with spironolactone alone pre-op

Algorithm for Primary Hyperaldosteronism



PHEOCHROMOCYTOMA

What is the epidemiology of pheochromocytoma?

- cause of HTN in ~0.1 to 0.6% of HTN'sives
- 95% sporadic, 5-10% familial (AD penetrance - chromosome 10)
- **25% found incidentally } 5% of all incidentalomas are pheo's**

Why is detection of a pheochromocytoma so important?

- physiologic effects of amines produced by lesion (epi, NE, dopamine)
- **smaller tumours release more catecholamines**
 - **bind + metabolize catecholamines poorly**
- peptides produced by amine precursor uptake and decarboxylation (APUD)-type cells
 - ACTH
 - calcitonin
 - β -endorphin
 - somatostatin
 - VIP
 - dynorphin
 - serotonin
 - neuropeptide
 - enkephalins
 - lipotropin

Signs and Symptoms

What is the most common sign of pheochromocytoma?

- **HTN → 80-90%**
 - majority have ≥ 1 episodes per week
 - sustained (kids, MEN II) in ~40%
 - paroxysmal (females) in ~50%
 - sustained + paroxysmal in ~60-65%

What are some other signs & symptoms of pheochromocytoma (CHART)?

→ **classic symptom triad is episodic H/A + tachycardia + diaphoresis**

→ symptoms

- **headache (2nd most common)**
- palpitations
- excessive sweating
- anxiety
- tremours
- chest or abdo pain
- N/V
- weakness

→ signs

- **HTN (most common)**
- tachycardia (or reflex bradycardia)
- pallor
- dilated pupils
- underweight
- psych changes
- tremor
- Raynaud's phenomenon

→ 75% have one or more episodes per week

→ can mimic hyperT4, pre-eclampsia, etc

Are there any stimuli that bring on attacks?

- certain postures
- exercise
- wearing tight clothes
- valsalva
- compression of tumour elicited by massage
- direct trauma
- foods rich in tyramine (beer, wine, cheese)
- meds → histamine, nicotine, glucagon, ACTH, β -blockers

What is the rule of 10's for pheochromocytoma?

- 10% normotensive
- 10% extra-adrenal } most common site is **organ of Zuckerkandl** (distal aorta @ bifurcation)
- 10% paediatric
- 10% malignant
- 10% multiple
- 10% bilateral
- 5-10% familial (AD inheritance – chromosome 10)
- 10% secretes mostly epinephrine (like the N adrenal) } Pheo usually secretes more NE

What is the DDX of pheochromocytoma (massive CHART)?

- hyperT4
- anxiety, tension, psychosis
- menopause
- migraine/cluster headaches
- acute hypertensive encephalopathy
- DM
- renal disease with HTN
- local arterial insufficiency of brain
- intracranial lesions
- autonomic hyperreflexia
- carcinoid
- hypoglycemia
- adrenocortical carcinoma
- pre-eclampsia/PIH
- MAOI induced HTN
- mastocytosis

List genetic syndromes associated with Pheo? }} “**2 MEN Take Violent Anal from Weber’s Nasty Penis**”

- 1) **MEN IIa (Sipple’s)** } pheo + medullary carcinoma thyroid (MCT) + PTH adenoma
- 2) **MEN IIb/III** } pheo + MCT + mucosal neuromas/GI ganglioneuromatosis
- 5) Tuberous sclerosis } seizures, MR, intracranial calcifications, Ash-leaf macules, AML, PCKD
- 3) **VHL type 2** } type 2A have RCC while type 2B do not
- 5) **Ataxia-telangiectasia** } cerebellar ataxia, telangiectasia of eyes, weak immune system, ↑’d AFP
- 6) **Sturge-Weber syndrome** } seizures, port wine stains, glaucoma, MR, cerebral AVMs
- 4) **Neurofibromatosis type 1 (von Recklinghausen’s)** } 1-2% (AD inheritance with café-au-lait spots, neurofibromas, Lisch nodules, optic gliomas, etc)
- 7) **hereditary Paraganglioma syndrome** } tumours of sympathetic & parasympathetic neuroendocrine system (head, neck, pheos, etc)

Table 53-18 -- Hereditary Forms of Pheochromocytoma

Syndrome	Gene	Chromosome Location
Multiple endocrine neoplasia type II	RET oncogene	10q11
von Hippel-Lindau disease	VHL tumor suppressor gene	3p25
Neurofibromatosis type 1	NF1	17q11
Hereditary paraganglioma syndrome	PGL1	11q23

From Pacak et al, 2001 .

What is the significance of pheochromocytoma & pregnancy?

- can mimic pre-eclampsia/PIH } PIH more likely if ++ proteinuria & symptoms in T3
- **diagnosis usually post-partum** → only 1/3 before delivery
- maternal & infant mortality rates >40%
→ highest rate of fetal loss in T1

What are some subsequent manifestations of pheochromocytoma (CHART)?

→ **from excess catecholamine secretion**

- CVA
- MI
- encephalopathy
- retinopathy
- CHF
- **catecholamine-induced cardiomyopathy** } **ALL PHEO PATIENTS NEED CARDIAC W/U**
- dissecting aneurysm
- ARDS
- shock
- renal failure or azotemia
- ischemic gut or megacolon
- azotemia

Children

What signs and symptoms are more common in kids with pheochromocytoma?

- **sustained HTN in 90%** → more commonly
- H/A
 - familial (10%)
- N/V
 - bilateral (24%)
- weight loss
 - extra-adrenal (15-30%)
- visual complaints
 - multiple (15-30%)
- polydipsia and polyuria
 - malignant
- convulsions

Laboratory Diagnosis

What lab tests are used to make a biochemical diagnosis of pheochromocytoma?

→ **these markers are elevated in ~95% of cases } 5% have normal studies**

- 1) 24hr urine → catecholamines
 - metanephrines
 - vanillylmandelic acid (**VMA – primary metabolite of catecholamines**)
- 2) serum → catecholamines } mostly NE (except Familial PHEO which is mostly Epi)
 - **metanephrines } most sensitive test (~99%)**

What is the upper limit of normal value of urine catecholamines & metabolites?

- catecholamines → epi 0.02mg/day
 - NE 0.08mg/day
 - total 0.1mg/day
- metanephrine → total 1.3mg/day
- VMA → 6.5mg/day

What drugs & substances can interfere with the urinary tests for pheochromocytoma (CHART)?

- | | |
|----------------------------|----------------------------|
| → increases apparent value | → decreases apparent value |
| - labetalol | - fenfluramine |
| - tetracycline | - ethanol |
| - erythromycin | - disulfiram |
| - chlormpromazine | - MAOIs |
| - ethanol | - clofibrate |
| - levodopa | |
| - MAOIs | |
| - benzo's | |

What is the role of the clonidine suppression test?

- to distinguish between pheochromocytoma and HTN'sive patient with slight elevation of catecholamines (neurogenic HTN)
- single dose 0.3mg po → measure plasma catecholamines 2-3 hrs after
- neurogenic HTN'sives will show a fall in plasma catecholamines (to below <500pg/mL)
- **pheo shows no fall in plasma catecholamines after clonidine**

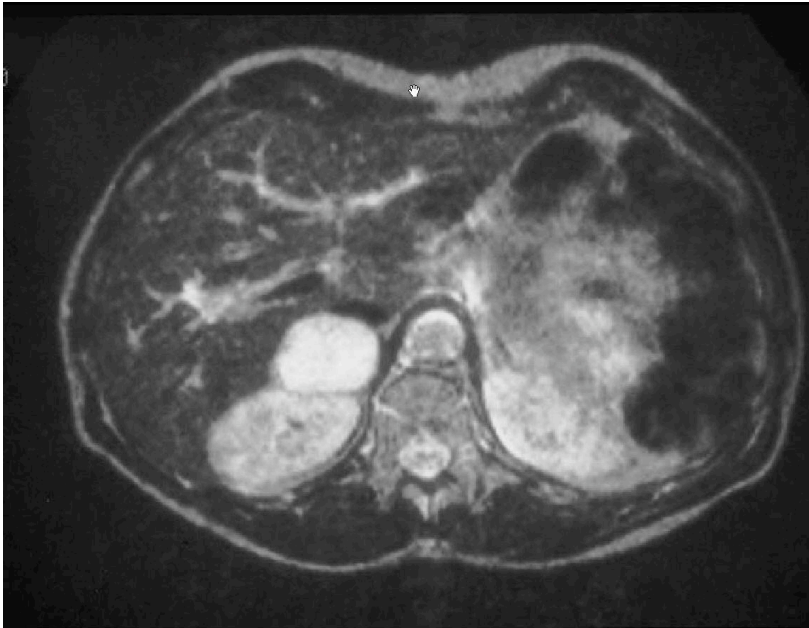
Radiologic Tests

What is the role of CT in diagnosing pheochromocytoma?

- 90% accuracy } does NOT differentiate pheo from other adrenal lesions
- } does NOT predict malignancy (other than size)

What is the role of MRI in diagnosing pheochromocytoma?

- **most sensitive test** } CONSIDER AS 1ST LINE IMAGING TEST (best overall sensitivity & specificity)
- characteristic “light bulb” appearance on T2 MRI } not always seen with new MRI
- NO dropout in out-of-phase imaging



→ T2 MRI OF PHEOCHROMOCYTOMA

What lesions are high intensity on T2-weighted MRI?

- adrenal carcinoma
- adrenal mets
- neural tumours
- PHEO
- cysts
- adrenal hemorrhage (most common after HIT, used to be after sepsis)

What is the indication to use MIBG scanning?

- 1) high index of suspicion but negative plasma or urine catecholamines and metabolites
 - 2) syndromes with pheochromocytoma (more likely to have extra-adrenal pheo's)
 - ¹³¹I-labeled MIBG
 - **more sensitive than CT in patients with extra-adrenal lesions**
 - **highly specific & good sensitivity → good screening test esp if CT and MRI are equivocal**
- contraindicated in pregnancy and if breast feeding

Preoperative Management

What is the management of pheochromocytoma?

- refer to anesthesia, endocrinology, cardiology
- surgical removal
 - except late pregnancy } α blockade (prazosin - phenoxy is teratogenic) until mature
 - } combined C/S + surgical removal → avoid stress of vag delivery

What is the pre-op management of pheochromocytoma?

- 1) long-acting α -blocker eg phenoxybenzamine (non-competitive/irreversible)
 - } start at 10-15mg po bid and increase by 10-20mg/day
 - } stop once BP stabilized with mild postural hypoTN or drop in Hct by ~5%
 - usually 40-100mg/day required
 - eg prazosin (competitive/reversible)
 - } good pre-op but can be overcome by surge of catecholamine during tumour manipulation
- 2) iv hydration } may need fluids d.t. expanded vascular bed from α -blockers
 - } give at least 1L of RL
- 3) β -blockers eg propranolol
 - } protect against arrhythmias and allows decreased dosage of α -blockers
 - } **SHOULD ONLY BE GIVEN AFTER α -BLOCKER RX ESTABLISHED**
 - β -blocker alone results in severe HTN from elevated PVR from unopposed α -adrenergic activity
 - } usually 20-40mg po tid
- 4) α -methylparatyrosine } recommended in addition to phenoxybenzamine/propranolol
 - } **mainly for patients with myocardiopathy, resistance to α -blockers**
 - } decreases rate of catecholamine synthesis (adrenolytic)
 - } S/Es → stones, sedation, diarrhea, anxiety, extrapyramidal signs
 - } 0.5 – 1.0g po tid

Anesthetic Management

What are the important anesthetic issues during surgical removal of a pheochromocytoma?

- **key is the management of the CV system**
- 1) art line + central line +/- Swan-Ganz
 - 2) combine intravenous agent and inhalation agent for induction of GA
 - **preferred anesthetic is THIOPENTAL followed by ISOFLURANE**
 - may have marked HTN on induction } phentolamine (short-acting α -blocker)
 - } nitroprusside, labetalol for severe HTN
 - 3) HTN'sive episodes and arrhythmias may occur during manipulation of tumour
 - lidocaine for ventricular arrhythmia
 - esmolol, propranolol for sinus tachycardia
- **watch for HYPOTENSION after removal of tumour } use NE**

Which anesthetic agents & drugs should be AVOIDED during adrenalectomy for pheochromocytoma (CHART)?

- | | |
|---|------------------------------|
| → inhalation agents } halothane | → pressors } ephedrine |
| → intravenous agents } propofol | → adjuvants } chlorpromazine |
| } ketamine | } metoclopramide |
| → narcotics } morphine | |
| → local anesthetics } cocaine | |
| → muscle relaxants } pancuronium | |
| } atracurium | |
| } tubocurarine | |

Post-op Management

What issues can result post-op after removal of a PHEO?

- 1) hypoTN } usually hypovolemia
- 2) HTN } catecholamine levels may remain elevated for a few days
→ may be residual un-resected tissue
- 3) hypoglycemia } elevated insulin

What is the long-term care after removal of pheochromocytomas?

- BP q3months x1yr, then can increase interval
- urine metanephrine q6months x2 yrs, then q1yr x 3yrs
- monitor for life if child
- especially for syndromes with pheo

MALIGNANT PHEOCHROMOCYTOMA

How do you determine if a pheo is malignant?

→ **10-20% are malignant**

- usually larger → >5cm
- more common in extra-adrenal tumours (eg paragangliomas)
- more common in kids
- no good markers → Ki-67, p53, telomerase activity

Where are the common sites of mets?

- 1) bone
- 2) liver
- 3) regional LNs
- 4) lung
- 5) peritoneum

What is the treatment of malignant pheochromocytoma?

- wide resection + adjacent organs involved
- debulking recommended even if not curative → decreases symptoms of catecholamine excess
- chemo → reports of partial responses only (neuroblastoma regimes)
- radioactive MIBG → reports of partial responses
→ for patient with abN MIBG studies

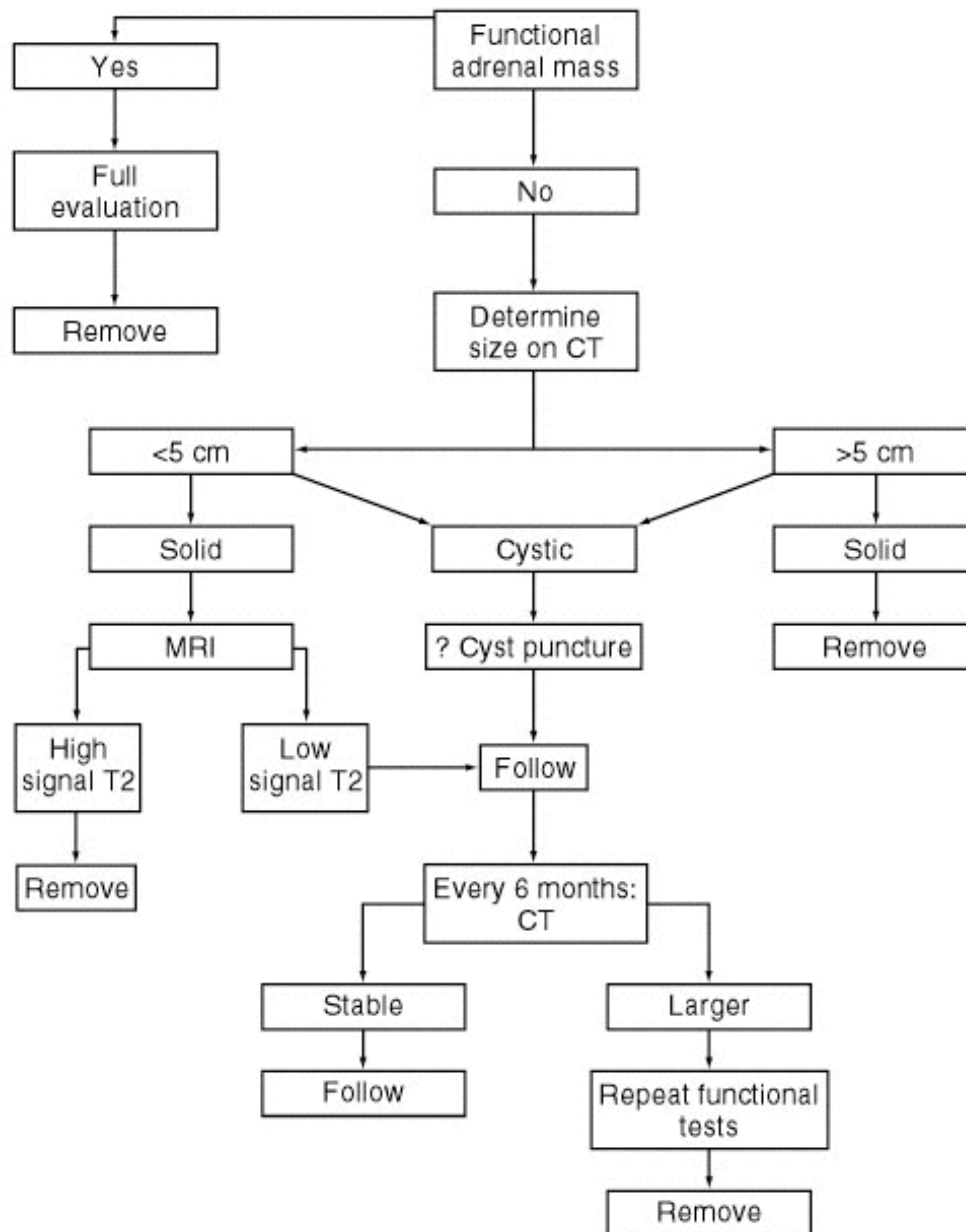
INCIDENTAL ADRENAL MASS

What are the findings of the NIH 2002 consensus on adrenal incidentalomas?

- 1) 75% of adrenal incidentalomas in patients with cancer are mets
- 2) 66% of adrenal incidentalomas in patients without cancer are benign
- 3) adrenal carcinomas account for 2% of lesions <4cm, 6% of lesions 4-6cm, and 25% of lesions >6cm
- 4) lesion >6cm is adrenal carcinoma until proven otherwise and should be removed
- 5) risk of malignancy of adrenal lesion <6cm is 1 in 1000
- 6) 20% of lesions <6cm develop hormonal hyperfunction (especially if >3cm)

What is the algorithm for evaluating an incidental adrenal mass?

→ IS IT FUNCTIONAL → IS IT MALIGNANT



What are the 3 first line functional/biochemical tests for an adrenal mass?

→ required in all incidentalomas

- | | |
|--|---|
| 1) urine catecholamines, metanephrines | } PHEO if +ve |
| 2) 1mg DST (or 24hr urine free cortisol) | } Cushing's if cortisol still ↑ |
| 3) serum K + aldosterone/PRA ratio if HTN'sive | } hyperaldosteronism if hypoK & ↑'d ARR |
| +/- 4) 17-OH ketosteroids and DHEAS | |

What is the main controversy in adrenal incidentalomas?

→ nonfunctioning, solid, adrenal mass 4-6cm

- 1) functional → treated based on Dx
- 2) <4cm → serial imaging q6months *** some advocate removal of all lesions >3cm ***
→ should recheck biochemical status annually for 4-5 yrs (20% become functional)
- 3) >6cm → remove

What can help to confirm the Dx of adrenal carcinoma in lesions that are 4-6cm in size?

- FNA Bx → nondiagnostic in ~30%
→ if diagnostic though, accurate in >95%
- MRI → high intensity in T2 more likely ACC } not specific though

What lesions are high intensity on T2-weighted MRI?

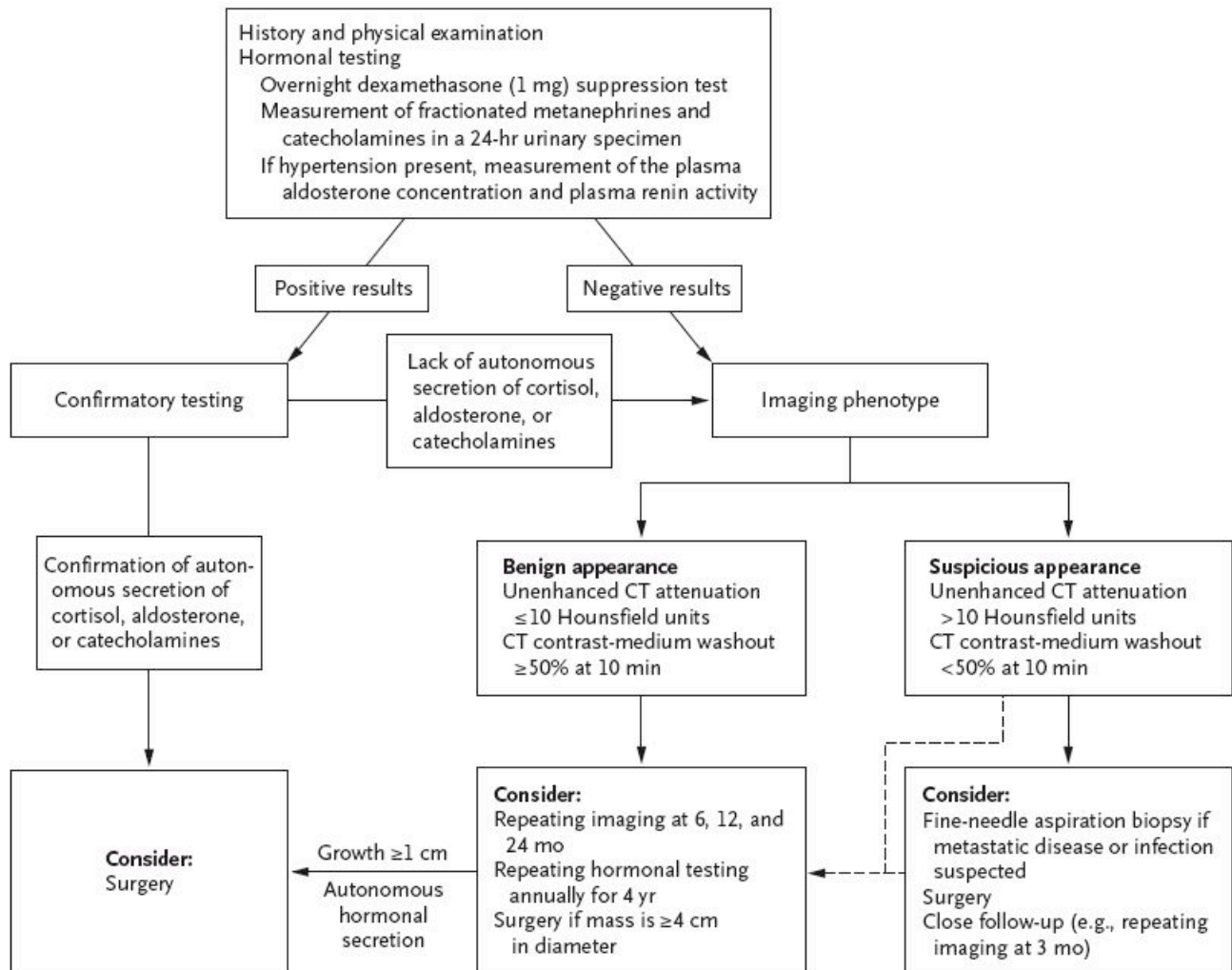
- 1) adrenal carcinoma
- 2) adrenal mets
- 3) neural tumours
- 4) PHEO
- 5) cysts
- 6) adrenal hemorrhage (now most commonly from HIT, not sepsis)

What is the DDx of an adrenal incidentaloma?

- 1) benign
 - cyst (endothelial/lymphangiomatous cysts & pseudocysts most common)
 - hemorrhage
 - abscess
 - myelolipoma
 - adenoma +/- secreting (Pheochromocytoma, Cushings) } adenoma most common adrenal mass
 - hyperplasia
 - oncocytoma
- 2) malignant
 - primary
 - non-functional adrenal carcinoma
 - estrogen-secreting adrenal cortical tumour \ T-secreting carcinoma is
 - aldo-secreting adrenal carcinoma / extremely rare
 - malignant Pheo
 - functional
 - secondary (MOST COMMON ADRENAL MALIGNANCY OVERALL)
 - melanoma, lung, breast (>50%)
 - RCC (40%)

What is the DDx for bilateral adrenal masses? }}} "Mets PITCH Last"

- Mets or malignancy
- Pheochromocytoma (10% bilateral)
- Infection
- TB (or any granulomatous disease)
- CAH
- Hemorrhage (most common with HIT, sepsis is 2nd)
- Lymphoma (Hodgkins)



→ NEJM (Young Jr – '07)

Table 3. Characteristics of Adrenal Incidentalomas on Imaging (Imaging Phenotype).*

Variable	Adrenocortical Adenoma	Adrenocortical Carcinoma	Pheochromocytoma	Metastasis
Size	Small, usually ≤ 3 cm in diameter	Large, usually > 4 cm in diameter	Large, usually > 3 cm in diameter	Variable, frequently < 3 cm
Shape	Round or oval, with smooth margins	Irregular, with unclear margins	Round or oval, with clear margins	Oval or irregular, with unclear margins
Texture	Homogeneous	Heterogeneous, with mixed densities	Heterogeneous, with cystic areas	Heterogeneous, with mixed densities
Laterality	Usually solitary, unilateral	Usually solitary, unilateral	Usually solitary, unilateral	Often bilateral
Attenuation (density) on unenhanced CT	≤ 10 Hounsfield units	> 10 Hounsfield units (usually > 25)	> 10 Hounsfield units (usually > 25)	> 10 Hounsfield units (usually > 25)
Vascularity on contrast-enhanced CT	Not highly vascular	Usually vascular	Usually vascular	Usually vascular
Rapidity of washout of contrast medium	$\geq 50\%$ at 10 minutes	$< 50\%$ at 10 minutes	$< 50\%$ at 10 minutes	$< 50\%$ at 10 minutes
Appearance on MRI†	Isointense in relation to liver on T_2 -weighted image	Hyperintense in relation to liver on T_2 -weighted image	Markedly hyperintense in relation to liver on T_2 -weighted image	Hyperintense in relation to liver on T_2 -weighted image
Necrosis, hemorrhage, or calcifications	Rare	Common	Hemorrhage and cystic areas common	Occasional hemorrhage and cystic areas
Growth rate	Usually stable over time or very slow (< 1 cm per year)	Usually rapid (> 2 cm per year)	Usually slow (0.5 cm to 1.0 cm per year)	Variable, slow to rapid

→ NEJM (Young Jr – '07)

SURGERY (Chapt 54)

What are the indications for adrenalectomy (CHART)?

- primary hyperaldosteronism } solitary adenoma (Conn's), primary adrenal hyperplasia
→ bilateral adrenal hyperplasia (meds 1st line)
- Cushing's syndrome (adenoma)
- pheochromocytoma
- adrenocortical carcinoma
- functional adrenal adenoma
- myelolipoma (symptomatic or pure lipoma)
- adrenal cyst
- metastatic tumour
- neuroblastoma (pediatric)
- incidental adrenal mass > 6 cm or growing adrenal lesions

What are the indications for open adrenalectomy?

→ lap adrenalectomy contraindicated if:

- 1) adrenocortical carcinoma with evidence of extra-adrenal invasion of adjacent organs
- 2) extension of adrenal vein tumour thrombus into IVC
- 3) symptomatic adrenal mass in pregnant patients

→ pre-op CT can help distinguish invasive from noninvasive adrenal carcinoma

What are the indications for partial adrenalectomy?

- solitary adrenal gland
- bilateral disease
- multiple adrenal tumours (eg VHL type2)

What are the contraindications to adrenalectomy?

→ absolute

- severe coagulopathy
- poor cardiopulmonary performance status
- known adrenal vein or IVC involvement (lap only)

→ relative for lap adrenalectomy

- previous open sx } could do retroperitoneal lap or even transthoracic lap
- tumour size } risk of carcinoma is the issue
 } some recommend 12cm max
- obesity } may need longer ports and instruments
- adrenal cortical carcinoma } risk of +ve margins and local recurrence

What are the key pre-op issues before adrenalectomy (CHART)?

→ primary hyperaldosteronism

- K supplementation
- BP control

→ Cushing's syndrome

- inhibition of cortisol production if severe symptoms } metyrapone
- control of DM
- correction of electrolyte abN's
- pre-op Abx
- operative stress steroids

→ adrenal carcinoma

- consent for possible adjacent organ removal
- r/o IVC or adrenal vein involvement

→ pheochromocytoma

- pre-op catecholamine blockade } α -blockade with phenoxybenzamine
 } consider β -blocker (propranolol)
 } consider methylparatyrosine

- volume expansion

- anesthesia consult } cardiac w/u to r/o catecholamine-related cardiomyopathy

→ adrenal incidentaloma

- anesthetic preparation for pheo } 5% have normal studies

What are some special considerations with regards to adrenalectomy?

1) kids } neuroblastoma is most common adrenal tumour & these tend to be large, infiltrative tumours
→ lap adrenalectomy difficult

2) pregnancy } must distinguish pheo (no proteinuria) from pregnancy-induced HTN (T3)
 } if pheo Dx'd in 3rd trimester, meds until C-section
 } if pheo Dx'd in 1st or 2nd trimester, must balance risk of surgery vs risk of pheo
 } evidence that laparoscopic surgery safe in pregnancy

3) partial adrenalectomy } usually performed with an endoscopic stapler
 } dividing adrenal vein doesn't affect viability of remaining adrenal

What are the potential complications of adrenalectomy?

→ INTRA-OPERATIVE (includes CHART)

- 1) hemorrhage } adrenal vein, IVC, lumbar vein, renal vein
 } most common complications in lap adrenalectomy (~50%) and the most common reason for open conversion (30%)
- 2) vascular injury } ligation of renal artery branch
 } ligation of SMV
 } ligation of mesenteric artery
 } IVC involvement
- 3) adjacent organ injury } pneumothorax, pancreas, duodenum, liver, spleen, stomach, colon, kidney
- 4) anesthetic complications } fluctuations in BP (pheochromocytoma), arrhythmias

→ POST-OPERATIVE

- 1) generic complications
 - hemorrhage
 - DVT/PE/MI
 - hiccups
 - pancreatic leak
 - pneumonia
 - ileus/SBO/LBO
 - pancreatitis
 - pneumothorax
- 2) disease-specific complications
 - primary hyperaldosteronism
 - hypoK (continued loss post-op)
 - hyperK (lack of aldosterone from other adrenal)
 - Cushing's syndrome
 - addisonian crisis
 - fracture secondary to osteoporosis
 - hyperglycemia
 - poor wound healing
 - increased risk of infections
 - pheochromocytoma
 - hypotension secondary to α -blockade after removal of tumour

HTN

What is the DDX of HTN?

- 1) essential HTN (90%)
- 2) secondary HTN (mnemonic AORTTA)
 - Aortic coarctation
 - OCP & other meds (eg cortisol, mineralocorticoids, NSAIDS, cyclosporine, etc)
 - Renal causes (5%)
 - parenchymal (3%) } unilateral (TB, Page kidney, congenital hypoplasia, etc)
 vs bilateral (DM, PCKD, obstructive, etc)
 - vascular (2%) } intrinsic (atherosclerosis, fibromuscular dysplasia, etc)
 vs extrinsic (RPF, tumour involving pedicle, etc)
 - Thyroid (hyperT4)
 - Toxemia of pregnancy (pre-eclampsia)
 - Adrenal causes
 - Cushings
 - Primary hyperaldosteronism (eg Conn's, bilateral adrenal hyperplasia)
 - Pheo
 - PAH
 - adrenocortical carcinoma (functional)

What are the various MEN syndromes?

	→ all have autosomal dominant inheritance (“TP after PP” for I and II)
Men I (Wermer’s syndrome)	<ol style="list-style-type: none"> HyperPTH: 90%; Asymptomatic hyperCa is the most common manifestation pituitary tumours pancreatic islet cell tumors <ul style="list-style-type: none"> - 25% of these have stones or nephrocalcinosis - diffuse hyperplasia or multiple adenomas are more common than solitary adenoma
MEN II (Sipple’s syndrome) AD on chromosome 10 (RET)	<ol style="list-style-type: none"> HyperPTH: 25% medullary thyroid ca pheochromocytoma <ul style="list-style-type: none"> - usually multiple parathyroid glands are affected either w/ hyperplasia or multiple adenomas - hypercalcemia, NEPHROLITHIASIS, NEPHROCALCINOSIS OR CRF
MEN III (formerly MEN IIb)	<ol style="list-style-type: none"> medullary thyroid ca pheochromocytoma oral and intestinal ganglioneuromatosis (mucosal neuromas) thickened corneal nerves Marfanoid habitus

MEN I }}} PTH + Pituitary + Pancreatic

MEN II }}} PTH + Thyroid + Pheo

MEN II }}} Thyroid + Pheo + ganglioneuromas + marfanoid

Chapter #54 – Adrenal Surgery

SURGICAL ANATOMY

What are the borders of the adrenal gland?

- 1) right adrenal
 - liver anteriorly
 - IVC medially
 - kidney inferolaterally
 - diaphragm along superior & posterior
- 2) left adrenal (slightly closer to hilum than R)
 - aorta medially
 - stomach & body of pancreas anteriorly
 - kidney inferiorly
 - spleen superiorly
 - diaphragm posteriorly

What is the vasculature of the adrenal gland?

- 1) arterial supply
 - inferior phrenic (superior) } **MAIN SUPPLY**
 - aorta (middle)
 - renal artery (inferior)
- 2) venous supply
 - R drains into IVC } 5-10% have accessory veins that drain into R renal vein, R hepatic vein, or inferior phrenic vein
 - L drains into renal vein

What is the lymphatic drainage of the adrenal gland?

- lateral aortic LN chain that extends from diaphragm to ipsilateral renal artery

CLINICAL INDICATIONS AND SELECTION OF PATIENTS

What are the indications for adrenalectomy (CHART)?

- primary hyperaldosteronism } solitary adenoma (Conn's), primary adrenal hyperplasia
→ bilateral adrenal hyperplasia (meds 1st line)
- Cushing's syndrome (adenoma)
- pheochromocytoma
- adrenocortical carcinoma
- functional adrenal adenoma
- myelolipoma (symptomatic or pure lipoma)
- adrenal cyst
- metastatic tumour
- neuroblastoma (pediatric)
- incidental adrenal mass >6cm or growing adrenal lesions

What are the contraindications to adrenalectomy?

- absolute
 - severe coagulopathy
 - poor cardiopulmonary performance status
 - known adrenal vein or IVC involvement (lap only)
- relative for lap adrenalectomy
 - previous open sx } could do retroperitoneal lap or even transthoracic lap
 - tumour size } risk of carcinoma is the issue
 - } some recommend 12cm max
 - obesity } may need longer ports and instruments
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 - 2) extension of adrenal vein tumour thrombus into IVC
 - 3) symptomatic adrenal mass in pregnant patients
- pre-op CT can help distinguish invasive from noninvasive adrenal carcinoma

What are the indications for partial adrenalectomy?

- solitary adrenal gland
- bilateral disease
- multiple adrenal tumours (eg VHL type2)

What is the best open approach for adrenalectomy for the different diseases?

- primary hyperaldosteronism } posterior
 - } 11th rib (left>right)
 - } posterior transthoracic
- Cushing's adenoma } 11th rib
 - } thoracoabdominal (large)
 - } posterior (small)
- Cushing's disease (bilateral hyperplasia) } bilateral posterior
 - } bilateral 11th rib
- adrenocortical carcinoma } thoracoabdominal
 - } 11th rib
 - } transabdominal
- pheo } transabdominal chevron
 - } thoracoabdominal (large, usually right)
 - } 11th rib
- neuroblastoma } transabdominal
 - } 11th rib
- bilateral adrenal ablation } bilateral posterior

PRE-OP MANAGEMENT

What are the key pre-op issues before adrenalectomy (CHART)?

- primary hyperaldosteronism
 - K supplementation
 - BP control
- Cushing's syndrome
 - inhibition of cortisol production if severe symptoms } metyrapone
 - control of DM
 - correction of electrolyte abN's
 - pre-op Abx
 - operative stress steroids
- adrenal carcinoma
 - consent for possible adjacent organ removal
 - r/o IVC or adrenal vein involvement
- pheochromocytoma
 - pre-op catecholamine blockade } α-blockade with phenoxybenzamine
 } consider β-blocker & methylparatyrosine
 - volume expansion
 - anesthesia consult } cardiac w/u to r/o catecholamine- related cardiomyopathy
- adrenal incidentaloma
 - anesthetic preparation for phea } 5% have normal studies

OPEN ADRENALECTOMY

What are the approaches to open adrenalectomy?

- 1) transperitoneal } midline
 } subcostal
 } thoracoabdominal
- 2) retroperitoneal } flank
 } posterior lumbodorsal

What are the advantages & disadvantages of the different approaches to open adrenalectomy?

	ADVANTAGES	DISADVANTAGES
transperitoneal	<ul style="list-style-type: none"> - better exposure - good access to great vessels and retroperitoneum 	<ul style="list-style-type: none"> - prolonged ileus - difficult exposure in morbid obesity
retroperitoneal	<ul style="list-style-type: none"> - less post-op ileus - less morbidity 	<ul style="list-style-type: none"> - smaller operative exposure - fewer landmarks

*** see chapter for descriptions of flank, posterior lumbodorsal, subcostal anterior, and thoracoabdominal approaches ***

LAP ADRENALECTOMY

What are the approaches to laparoscopic adrenalectomy?

→ **Lap adrenalectomy is the standard of care, except for invasive adrenal carcinoma or adrenal carcinoma with IVC thrombus, or in pregnancy**

- 1) transperitoneal } anterior supine (good bilateral access)
 } flank/lateral (greater workspace)
- 2) retroperitoneal } flank/lateral

*** see chapter for descriptions of transperitoneal and retroperitoneal flank approach ***

HAND-ASSISTED SURGERY

What are the advantages & disadvantages of hand-assisted lap adrenalectomy?

→ ADVANTAGES

- tactile sensation
- faster dissection
- better control of bleeding complications
- shorter learning curve

→ DISADVANTAGES

- decreased field of view
- air leak from hand port

ROBOTIC SURGERY

Robot-assisted Lap adrenalectomy has been done } case reports

INTRA-OP ULTRASONOGRAPHY

What is the role for intra-op U/S?

- extracorporeal visualization of adrenal gland on U/S is very difficult
- intra-op U/S may help identify adrenal gland and/or adrenal vein in obese patients
- especially helpful in lap partial adrenalectomy

POST-OP MANAGEMENT

What is the post-op management after adrenalectomy?

- follow lytes the night of surgery and each morning } esp. for Conn's or Cushing's syndrome
- watch for Addisonian crisis } hypoTN, confusion, lethargy, N/V, abdo pain, fever
 } commonly seen after sx for Cushing's syndrome
- may need cortisol and mineralocorticoid (fludrocortisone) replacement
- adjustment of anti-HTN'sive meds may be needed

OUTPATIENT AND SHORT-STAY LAPAROSCOPIC ADRENALECTOMY

Discharge within 24hrs of surgery has been done safely

OUTCOMES

What is the data between lap and open adrenalectomy?

- no randomized prospective trials
- clear advantage with post-op pain, hospital stay, blood loss, and complication rate
- slightly longer OR time

What is the data between retroperitoneal and transperitoneal lap adrenalectomy?

- seems to favor retroperitoneal approach
- shorter OR time, less blood loss, less post-op analgesia, less GI issues, shorter hospital stay

COMPLICATIONS

What are the potential complications of adrenalectomy?

→ INTRA-OPERATIVE (CHART)

- 1) hemorrhage } adrenal vein, IVC, lumbar vein, renal vein
 } most common complication in lap adrenalectomy (~50%) and most common reason for open conversion (30%)
- 2) vascular injury } ligation of renal artery branch
 } ligation of SMV
 } ligation of mesenteric artery
 } IVC involvement
- 3) adjacent organ injury } PTX, pancreas, duodenum, liver, spleen, stomach, colon, kidney
- 4) anesthetic complications } severe fluctuations in BP (pheochromocytoma), arrhythmias

→ POST-OPERATIVE

- 1) generic complications
 - hemorrhage
 - DVT/PE/MI
 - hiccups
 - pancreatic leak
 - pneumonia
 - ileus/SBO/LBO
 - pancreatitis
 - pneumothorax
- 2) disease-specific complications
 - primary hyperaldosteronism
 - hypoK (continued loss post-op)
 - hyperK (lack of aldosterone from other adrenal)
 - Cushing's syndrome
 - Addisonian crisis
 - fracture secondary to osteoporosis
 - hyperglycemia
 - poor wound healing
 - increased risk of infections
 - pheochromocytoma
 - hypotension secondary to α -blockade after removal of tumour

Are complications more common with open adrenalectomy?

- YES } pulmonary, wound, and infectious complications were significantly higher with open sx
- fewer injuries to adjacent organs with lap sx
 - lap retroperitoneal approach may account for a lot of this
- also, there may be a selection bias } larger tumours approached open

SPECIAL CONSIDERATIONS

What are some special considerations with regards to adrenalectomy?

- 1) kids } neuroblastoma is most common adrenal tumour & these tend to be large, infiltrative tumours
 → lap adrenalectomy difficult
- 2) pregnancy } must distinguish pheo (no proteinuria) from pregnancy-induced HTN (T3)
 } if pheo Dx'd in 3rd trimester, meds until C-section
 } if pheo Dx'd in 1st or 2nd trimester, must balance risk of surgery vs risk of pheo
 } evidence that laparoscopic surgery safe in pregnancy
- 3) partial adrenalectomy } usually performed with an endoscopic stapler
 } dividing adrenal vein doesn't affect viability of remaining adrenal

What are the indications for partial adrenalectomy?

- solitary adrenal gland
 - bilateral disease
 - patients with familial syndromes
 → pheo in patients with VHL, familial pheochromocytoma, or MEN IIa
- endoscopic stapler used } can take adrenal vein without compromising remaining gland

NONSURGICAL ALTERNATIVES

What ablative technologies have been described to treat adrenal lesions?

- 1) RFA } mainly for adrenal mets, mets of adrenal carcinoma, or mets of malignant pheo
 } can result in severe HTN
 → unknown pheo or catecholamine release from thermal injury
 } avoid RFA if pheochromocytoma suspected
- 2) cryoablation } limited literature

Chapter #55 – Physiology and Pharmacology of the Renal Pelvis and Ureter

CELLULAR ANATOMY

What are the main components of the smooth muscle cell of the ureter?

- nucleus } DNA + nucleolus
- cytoplasm/sarcoplasm } mitochondria (energy)
- } endoplasmic reticulum and sarcoplasmic reticulum (Ca²⁺ storage)
- } actin and myosin (contractile proteins)

DEVELOPMENT OF THE URETER

What is the embryologic origin of the ureter?

- **arises as an outpouching from mesonephric duct**
- formation of ureteric bud and its subsequent branching is induced by several factors derived from the adjacent metanephrogenic mesenchyme
 - GDNF, TGF- β , HGF, FGF, heparin sulfate proteoglycans, laminins, integrins, MMPs
- ureteral bud branching is controlled by apoptotic pathways
 - caspase inhibitors can inhibit ureteral bud branching
- ureteral lumen obliterates at one point during development, then recanalizes again
 - angiotensin II, acting through AT₂ receptors, are involved in recanalization of ureter
- calcineurin is also important in development of renal pelvis, ureter, & ureteral smooth muscle

ELECTRICAL ACTIVITY

What are the basics of cell resting potential and depolarization?

- resting membrane potential } **determined mainly by K⁺** but Na also plays a role
 (RMP)
 - [K] is higher inside the cell & [Na] is higher outside the cell
 - } NA-K-ATPase maintains K and Na gradient
 - } ureteral smooth muscle cell RMP is -33 to -70mV
 - inside of cell membrane is more -ve than outside
- action potential } stimulus strong enough to decrease transmembrane potential to the threshold potential results in an action potential
 - **action potential is related to rise in intracellular Ca²⁺ & decreased membrane permeability to K⁺**
 - depolarization results in inside of cell membrane becoming less -ve than RMP
 - } once peak of action potential is reached, membrane maintains depolarized state (action potential plateau) for a period of time before repolarization occurs
 - action potential plateau is related to persistent influx of Ca²⁺ and Na⁺ influx
 - repolarization is related to renewed \uparrow in permeability to K⁺
 - } action potential can act as stimulus for excitation of adjacent resting cells
 - propagation of ureteral contraction

What is the origin of ureteral peristalsis?

- originates with electrical activity at pacemaker sites located at pelvicalyceal border
 - **minor calyx serves as site of primary pacemaker cells**
 - C-kit is important in development of pacemaker activity
- electrical activity is propagated distally } peristalsis – ureteral contraction
- efficient propulsion of urine depends on the ureter's ability to coapt its walls completely
- **latent pacemakers are found in all regions of ureter**
 - peristalsis still occurs after transection of ureter

How do pacemaker cells differ from other cells?

- RMP is less -ve & does not remain constant } undergoes slow spontaneous depolarization
- action potentials have a slower rate of rise and a lower amplitude
 - in upper urinary tract, related to opening and slow closure of voltage-activated L-type Ca^{2+} channels

CONTRACTILE ACTIVITY

What are the main steps involved in smooth muscle contraction responsible for ureteral contraction?

- increased free sarcoplasmic Ca^{2+} causes actin and myosin to contract
- higher concentration of Ca^{2+} results in formation of Ca^{2+} -calmodulin complex
- Ca^{2+} -calmodulin activates myosin light-chain kinase
- activated myosin light-chain kinase catalyzes phosphorylation of myosin light chain
- phosphorylated myosin light chain allows actin to activate myosin Mg^{2+} -ATPase
- activated myosin Mg^{2+} -ATPase leads to smooth muscle contraction
- different from skeletal muscle which involves increased Ca^{2+} that binds to troponin, thereby displacing tropomyosin, thus allowing actin and myosin to interact and contract
- Ca^{2+} -independent contraction is possible

What are the 2 sources of the increased Ca^{2+} responsible for ureteral smooth muscle contraction?

- 1) influx of extracellular Ca^{2+} through L-type Ca channels (major source of Ca^{2+})
- 2) intracellular Ca^{2+} release from endoplasmic or sarcoplasmic reticulum

What are the 2nd messengers involved in Ca^{2+} -related ureteral smooth muscle contraction?

- phospholipase C (PLC)
- inositol 1,4,5 trisphosphate (IP_3)
- protein kinase C (PKC)
- diacylglycerol (DG)

What are the factors important in ureteral relaxation?

- in response to β -agonists, Gs protein + Mg + GTP + adenylyl cyclase converts ATP to cAMP
 - **cAMP** responsible for smooth muscle relaxation
- increased Ca^{2+} leads to synthesis of NO, which activates guanylyl cyclase resulting in conversion of GTP to cGMP
 - involves nNOS, eNOS, and iNOS
 - **cGMP** responsible for smooth muscle relaxation
- **adenosine** also involved in relaxation of ureteral smooth muscle

MECHANICAL PROPERTIES

What are the mechanical factors involved in ureteral contraction?

- 1) force-length relations } depends on number of linkages between contractile proteins
→ actin and myosin
- 2) force-velocity relations } depends on rate of formation & breakdown of linkages b/w actin & myosin
- 3) pressure-length-diameter relations } result of longitudinal, circumferential, and spiral configuration of ureteral smooth muscle fibers

ROLE OF THE NERVOUS SYSTEM IN URETERAL FUNCTION

How is the ureteric smooth muscles innervated?

- syncytial type of smooth muscle } no discrete NMJ for each fiber
- depends on diffuse release of NT from a bundle of nerves with subsequent spread of excitation from one muscle cell to the next
- sympathetic & parasympathetic neurons involved
- **ureteral peristalsis can occur without innervation (latent pacemakers all throughout)**
- nervous system plays a modulating role in ureteral peristalsis

What is the effect of the parasympathetics on ureteral smooth muscle?

→ **cholinergics have excitatory effect } ↑'d frequency & force of peristalsis**

- ACh
- methacholine
- carbamylcholine
- bethanechol

What are the precursors to acetylcholine?

- acetyl CoA + choline -----→ Ach
choline acetyltransferase

What is the effect of anticholinesterases on the ureter?

- eg physostigmine, neostigmine
- increases duration and intensity of Ach action
- increased peristalsis

What is the effect of parasympatholytics on the ureter?

- eg atropine
- does NOT significantly decrease ureteral peristalsis } no benefit in ureteral colic

What is the effect of the sympathetics on ureteral smooth muscle?

- activation of α -adrenergics results in ureteral peristalsis } NE, phenylephrine
- activation of β -adrenergics tend to inhibit peristalsis } isoproterenol, orciprenaline

What is the effect of sympatholytics on the ureter?

- **α -blockers decrease ureteral peristalsis } ++ benefit in ureteral colic**
- β -blockers block inhibitory effects of β -adrenergics on ureteral peristalsis

What is the role of sensory nerves in ureteral contraction?

- tachykinins stimulate ureteral contraction } eg substance P, neurokinin A, neuropeptide K
→ more prominent in renal pelvis
- calcitonin gene-related peptide (CGRP) inhibits ureteral contraction
→ more prominent in ureter

URINE TRANSPORT

How is urine transported out of the renal pelvis?

- N urine flows } calyceal & renal pelvic contractions >> upper ureteral contractions
 - } ureteral contractile pressures >> renal pelvic pressures
 - } relative block of electrical activity at UPJ
 - renal pelvis fills and pressure rises until urine extrudes into upper ureter
 - closed UPJ may protect kidney in dissipating backpressure from ureter
- high flow rates } block at UPJ ceases and calyceal & pelvic ctns = ureteral ctns

How is urine transported down the ureter?

- N urine flows } contraction wave proximal to urine bolus propels urine down to bladder
 - } efficient transport of urine requires complete coaptation of ureteral walls
- high flow rates } ureteral walls don't coapt
 - } continuous column of fluid transported, NOT boluses of urine
 - increases in urine flow result in increased frequency of peristalsis

What is ureteral pressure during urine transport?

- resting baseline pressure } 0-5cm H₂O
- ureteral contractions } 20-80cm H₂O → occurs at 2-6 times per minute
- **normal renal pelvic pressure is ~6.5 mmHg**

How does intravesical pressure affect urine transport in the upper tracts?

- N urine flow } ureteral contractile pressure must exceed bladder pressure
- high flow rates } baseline pressure in column of urine within ureter must exceed intravesical pressure
- **intravesical pressures ≥40 cm H₂O leads to ureteral decompensation & chronically can lead to upper tract deterioration**

What are the 3 potential impediments of efficient urine bolus transfer across the UVJ into the bladder?

- 1) UVJ obstruction
- 2) excessively high intravesical pressure
- 3) high urine flow rates that exceed transport capacity of normal UVJ

PATHOLOGIC PROCESSES AFFECTING URETERAL FUNCTION

What are the effects of obstruction on ureteral function?

- depends on degree & duration of obstruction, rate of urine flow, and presence of infection
- obstructed ureter can't coapt ureteral wall & can't generate N active intraluminal pressures
- increased resting ureteral intraluminal pressure initially
 - ureteral pressure reaches maximum ~3hrs
 - declines afterwards to a little above baseline and then plateaus } remains ↑'d longer in BUO
 - due to reduced RBF, GFR, pyelovenous reabsorption, etc
 - resting ureteral pressures can't differentiate obstruction from non-obstructive dilation
- gradual increase in ureteral length and diameter
 - occurs even once ureteral pressure plateaus } "creep" seen in viscoelastic structures
 - Laplace's law } increased diameter related to decreased pressure
- also get a transient increase in amplitude & frequency of peristaltic contractions
 - as urine fills ureter, however, contractions become smaller and coaptation does not occur
 - urine transport then becomes dependent on hydrostatic forces generated by kidney
- ureteral smooth muscle hypertrophy occurs over time
 - potential for increased contractility } this is offset by dilation & thinning of muscle though
 - N ureteral peristalsis can occur after relief of obstruction <2wks
- presence of infection impairs urine transport by decreasing ureteral contractions

How does obstruction affect the upper tract on the cellular level?

- increase in type 1 & type 3 collagen
- increased ratio of collagen:smooth muscle
- alters coordinated pacemaker cells in renal pelvis

What are the 3 main factors implicated in the development of VUR?

- 1) anatomical and functional abnormalities of UVJ (primary)
- 2) significantly high intravesical pressures (secondary)
- 3) impaired ureteral function

What are the 5 main factors that affect spontaneous stone passage?

- 1) size & shape of stone
- 2) intrinsic areas of narrowing within ureter (eg UVJ, pelvic brim, UPJ)
- 3) ureteral peristalsis
- 4) hydrostatic pressure of column of urine proximal to stone
- 5) edema, inflammation, spasm of ureter at site of stone impaction

What are the 2 most important factors in facilitating stone passage?

- 1) increase in hydrostatic pressure proximal to stone
- 2) relaxation of ureter in region of stone

EFFECT OF AGE ON URETERAL FUNCTION

How does age affect ureteral function?

- neonates & children } more significant degree of ureteral dilation in response to obstruction
 - } increased force of ureteral contractions between 3wks and 3 months
 - no increase in rate of peristalsis during this period
- older age } decrease in ureteral relaxation in response to β -agonists (less cAMP with age)

EFFECT OF PREGNANCY ON URETERAL FUNCTION

What are the effects of pregnancy on ureteral function?

- hydroureteronephrosis } starts in T2 and subsides by first month after parturition
 - } mainly mechanical (uterus) ... ?? hormonal also (progesterone)

What findings support a mechanical cause of hydroureteronephrosis of pregnancy?

- 1) worse on R side
- 2) elevated resting ureteral pressures above pelvic brim that improves when positional changes allow the uterus to fall away from the ureters
- 3) normal ureteral contractile pressures
- 4) no hydro of pregnancy in those with conduits or pelvic kidneys
- 5) no hydro of pregnancy in quadrupeds (uterus hangs away from ureters)

EFFECT OF DRUGS ON THE URETER

Which drugs stimulate ureteral activity (INCREASED CONTRACTIONS)?

- 1) narcotics } if anything, they stimulate ureteral contractions
→ use in renal colic is related to decreased CNS pain perception
→ not a local effect
- 2) angiotensin } increases ureteral contractions
- 3) endothelins } increases contractions (potent vasoconstrictor)
- 4) histamines } mostly increases peristalsis (mediated by H₁ receptors)
} can also cause ureteral relaxation (mediated by H₂ receptors)
- 5) kinins } increases frequency of ureteral contractions
- 6) ABx } most cause ureteral relaxation but a few cause contraction
→ tetracycline
- 7) cholinergics (eg bethanecol)
- 8) anticholinesterases (eg neostigmine) } perpetuates cholinergic effects
- 9) β -blockers

Which drugs inhibit ureteral activity (DECREASED CONTRACTIONS)?

→ “Not Action PACK”

- 1) NSAIDs } decreases PG-mediated ureteral contractions
→ good for renal colic
} prevents PG-mediated vasodilation
→ decreases RBF & urine production, leading to lower intra-ureteral pressures
- 2) α -blockers
- 3) Progesterone
- 4) ABx } most decrease ureteral contractions
→ eg ampicillin, gentamicin
- 5) CCB } decrease ureteral contractions
- 6) K⁺ channel openers } inhibits renal pelvic and ureteral contractions
→ eg TCAs (amitriptyline)

What are the effects of 5-HT and cardiac glycosides on ureteral function?

- serotonin } can stimulate, inhibit, or have no effect on ureteral contractions
- cardiac glycosides } depends on species, but can cause increased & decreased contractions

Chapter #56 – Bladder and Urethral Physiology and Pharmacology

RELEVANT ANATOMY AND BIOMECHANICS

What are the 3 main layers of the bladder wall?

- transitional epithelium → 6 cells thick and sits on BM
- lamina propria → thick layer of fibroelastic connective tissue
→ contains blood vessels & smooth muscle fibers (muscularis mucosa)
- muscularis propria (detrusor) → arranged into **inner longitudinal, middle circular, outer longitudinal layers** (clearly separated at BN, indiscernable at dome)

Describe the trigone of the bladder.

- triangle of smooth muscle between ureteric orifices and the internal urethral meatus
- contain fibers of longitudinal smooth muscle from ureter which are thickened along the interureteric ridge (Mercier's bar) and between the ureters and the meatus (Bell's muscle)
- muscle of trigone forms 3 distinct layers;
 - 1) superficial layer → from longitudinal inner muscle of ureter
→ extends down male urethra to insert at verumontanum
 - 2) deep layer → continuation of Waldeyer's sheath that inserts at bladder neck
 - 3) detrusor layer → outer longitudinal and middle circular smooth muscle layers of bladder wall (predominantly circular)

Describe the male & female bladder neck musculature.

- men → inner longitudinal fibers become inner longitudinal layer of smooth muscle in urethra
→ middle circular layer forms a circular preprostatic sphincter (BN continence) that is richly innervated by adrenergic fibers (sympathetics)
→ outer longitudinal fibers well developed only on posterior aspect of bladder base to provide a strong trigonal backing
- women → inner longitudinal fibers converge and become inner longitudinal layer of urethra
→ poorly developed, if not non-existent, middle and outer layers
→ very little adrenergic innervation of bladder neck with limited sphincteric fxn

What is the blood supply of the bladder?

- superior & inferior vesical arteries (anterior branch of internal iliac)
- can also receive blood from any adjacent branch of internal iliac
- lateral and posterior pedicles
→ lateral and posterior vesical ligaments in men
→ cardinal and uterosacral ligaments in women
- veins drain into internal iliac

What is the lymphatic drainage of the bladder?

- **mostly to external iliac nodes**
- some to internal iliac & obturator nodes, and some even to common iliac and pre-sacral nodes

What is the innervation of the bladder?

- **autonomic afferent fibers pass from pelvic plexus**, via lateral & posterior pedicles, to bladder
→ **parasympathetics travel via cardinal ligaments in F**
- bladder wall is richly supplied by parasympathetic cholinergic receptors but has very little sympathetic adrenergic receptors
→ **M2 >>> M3 receptors } but M3 receptors more involved in bladder contraction**
- a special non-adrenergic, non-cholinergic (NANC) component participates in bladder activity
but the neurotransmitter hasn't been identified
- male BN is richly supplied with sympathetic α -adrenergic receptors
- **afferent fibers travel via hypogastric nerves (w/ sympathetics) AND via pelvic nerves (w/ parasympathetics)**

What is Laplace's Law?

- $T = \frac{P_{ves} \times R}{2d}$
 - } P_{ves} = intravesical pressure
 - } T = wall tension
 - } R = bladder radius
 - } d = wall thickness
- \ bladder wall tension is a function
/ of intravesical pressure,
/ bladder size & wall thickness

Which bladder components contribute to the viscoelastic behaviour of the bladder?

- urothelium
- smooth muscle
- stroma } ~50% collagen
 - type 1 & type 3 collagen are the most common (also see type 4)
 - higher collagen:smooth muscle ratio (esp type 3) assoc'd w/ poor compliance
- } ~2% elastin

What is bladder compliance?

- Bladder compliance = $\frac{\text{change in volume}}{\text{change in pressure}}$
 - combination of muscle & connective tissue spatial changes is required to accommodate urine at low intravesical pressures during filling
 - lamina propria thins faster than muscle
 - detrusor muscle shifts from top-to-bottom to a side-to-side configuration
 - coiled type 3 collagen fibers elongate and assume a more parallel orientation

Why can women void even with low P_{det} ?

- with open urethra & high urine flow, bladder can empty with little P_{det}
 - low voiding pressure in F does not equate to impaired detrusor contractility
- \ P_{det} reflects outlet
/ resistance

THE URINARY BLADDER

What is the function of the bladder?

- 1) urine storage } must be compliant and allow increase in volume without significant rise in pressure
- 2) urine emptying } synchronous contraction of smooth muscle against low resistance

What are the main differences between smooth muscle & skeletal muscle?

- 1) **smaller spindle-shaped cells** w/ contractile proteins (actin & myosin) that are **NOT arranged in regular sarcomere pattern**
 - variable matrix of actin & myosin
- 2) smooth muscle maintains a steady level of tension
 - **modulated by hormones**, local factors (eg NO), or by autonomic nerves
- 3) smooth muscle is more adaptable and is able to adjust its length over a much wider range
 - **can change muscle length by 75% (vs ~30% for skeletal muscle)**
 - huge volume differences (5cc vs 1000cc)

Table 56-1 -- Comparison of the Properties of Skeletal and Smooth Muscle

Property	Skeletal Muscle	Smooth Muscle
Cell characteristics	Very long cylindrical cells with many nuclei	Spindle-shaped cells with a single nucleus
Maximum cell size (length × diameter)	30 cm × 100 μm	200 μm × 5 μm
Visible striations	Yes	No
Ultrastructure	Sarcomere pattern	No sarcomere pattern
	No immediate filaments	Intermediate filaments
		Dense bodies
Motor innervation	Somatic	Autonomic
Type of contracture	Phasic	Mostly tonic, some phasic
Contractile activity	Disinhibition of tropomyosin	Active myosin phosphorylation
	Sliding filaments	? Sliding filaments
	Rapid contraction	Formation of "latch state"
Calcium regulation	Rapid Ca ²⁺ influx via T tubule	Voltage- and receptor-operated Ca ²⁺ channels
		Release from internal stores
Basic muscle tone	Neural activity	Intrinsic, extrinsic factors
Force of contraction regulated by hormone	No	Yes

How does bladder smooth muscle contraction work?

→ stretched myocytes during filling can lead to contraction of some individual cells

→ **coordinated emptying only occurs in response to ACh released from parasympathetics**

- muscarinic M₃ receptors induce ctns via influx of Ca²⁺ through nifedipine-sensitive L-type Ca channels
- Ca²⁺ binds to calmodulin → activated calmodulin activates myosin light-chain kinase → activated kinase enzyme phosphorylates myosin allowing interaction with actin

Why is detrusor smooth muscle less well coupled electrically compared to other smooth muscles?

→ no fused tetanic contractions

- poor coupling prevents synchronous activation of smooth muscle cells during filling
- some degree of coupling req'd for emptying } interstitial cells may help propagate signal b/w muscles
→ abN interstitial cells may act as spontaneous pacemakers and play a role in OAB

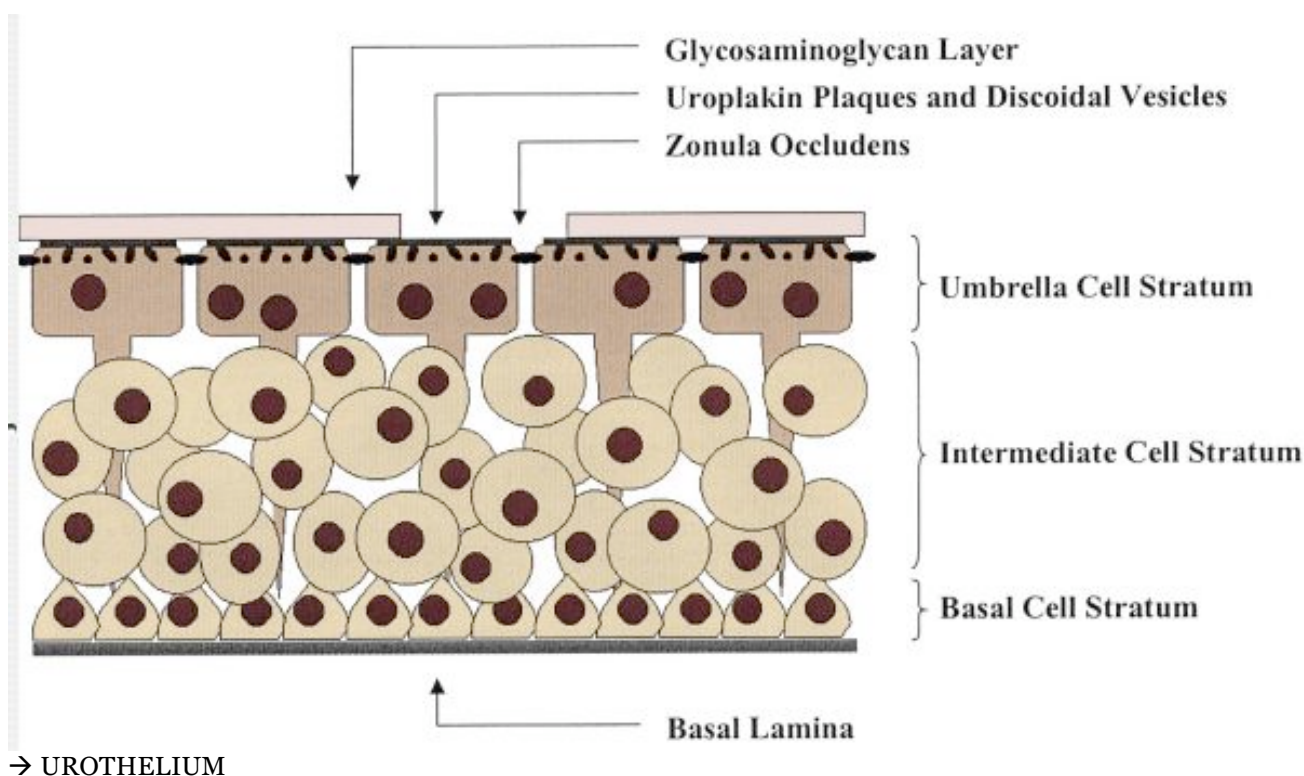
How does bladder wall ischemia affect function?

- **blood flow decreases with distension } normal**
- with poor compliance, high wall tension reduces blood flow and ischemia can develop
- chronic ischemia can lead to damaged nerves and smooth muscle in the bladder wall

What are the layers of the bladder urothelium?

→ **normally ~6 cells thick**

- 1) umbrella cells } largest epithelial cells in human body (100-200μm)
 } GAG layer
- 2) intermediate cells
- 3) basal cells



What is the role of the glycosaminoglycan (GAG) layer of the urothelium?

- serves as bacterial anti-adherence layer
- prevents urothelial damage by large macromolecules
- controversy re: role as primary epithelial barrier b/w urine & plasma } likely not

What is the function of the umbrella cells?

- forms primary urine-plasma barrier
- have ability to increase & decrease surface area } primarily at luminal surface
- multi-nucleated cells
- asymmetrical lipid bilayer } lipid + protein plaque outer leaflet
 - uroplakin 1a, 1b, 2, 3 } attachment site of type 1 piliated *E. coli*
 - } lipid inner leaflet

What are the main factors that influence urothelial permeability?

- 1) passive diffusion
 - cystitis results in increased permeability to water and urea
- 2) osmotically driven diffusion
 - urothelium maintains osmotic gradient between plasma and urine
 - hyperosmolar solutions can excite afferent nerves
 - changes in osmolality, pH, & ionic composition of urine can influence detrusor activity
- 3) active transport
 - Na^2+ is actively transported across urothelium
- 4) inertness of membrane to solutes

THE URETHRA

What type of musculature is found in the urethra?

- striated muscle } forms a rhabdosphincter in wall of urethra in circular configuration
 - } horseshoe shaped (deficient posteriorly)
 - } distinct from periurethral skeletal muscle of pelvic floor
 - male } extends from bladder base and anterior prostate to the full length of the membranous urethra
 - female } extends from proximal urethra distally
 - smooth muscle } thinner than in bladder
 - } inner longitudinal layer (thick) + outer circular layer (thin)
- both striated and smooth muscles play a role in urethral tone
→ blocking striated muscle w/ nicotinic neuromuscular blockers reduces urethral tone by ~40%
→ blocking sympathetics with α -blockers may reduce urethral pressure by ~33%

What constitutes the EUS?

- striated muscle of distal rhabdosphincter + periurethral striated muscle of pelvic floor
- has some smooth muscle also

How is continence maintained in women?

- 1) passive **transmission of abdominal pressure** to proximal urethra
 - pressure transmission presses anterior wall against posterior wall
 - rigid posterior wall requires good pelvic support from muscle and connective tissues
- 2) active contraction of **striated muscle of EUS** (guarding reflex)
 - active urethral continence (neural)
- 3) **pubourethral attachments** and vaginal connections to pelvic muscles & fascia compress the urethra against the pubis during filling and straining

What type of fibers are found in the EUS?

- striated muscle of distal rhabdosphincter } mainly slow-twitch
 - in male, 65% slow-twitch
 - in female, 87% slow-twitch
- periurethral striated muscle } fast-twitch + slow-twitch

NEURAL CONTROL OF THE LOWER URINARY TRACT

What is the innervation of the lower urinary tract?

- 1) **sympathetics** } thoracolumbar nerves (**T10-L2**) travel via **hypogastric plexus**
 - inhibits bladder
 - excites BN and urethra

} afferents are in **rostral lumbar dorsal root ganglia**
- 2) **parasympathetics** } **pelvic nerves (S2-S4)**
 - excites bladder
 - relaxes urethra

} postganglionic neurons found in detrusor wall AND pelvic plexus
→ cauda equina or pelvic plexus injury \neq complete denervation

} **afferents are in sacral dorsal root ganglia** & travel up Lissauer's tract
- 3) **somatics** } **pudendal nerves (S2-S4)**
 - excites EUS } also excites bulbospongiosus & ischiocavernosus muscles

} motoneurons are found in lateral border of ventral horn (**Onuf's nucleus**)
} **afferents are in sacral dorsal root ganglia** & travel up Lissauer's tract

What occurs during bladder filling?

- low and relatively constant bladder pressures during filling
- primarily a passive phenomenon dependent on intrinsic properties of bladder smooth muscle and inactive parasympathetic efferents
- bladder to sympathetic reflex also promotes closure of urethral outlet and inhibits bladder contractions
- increased pudendal nerve activity stimulates EUS contraction
- contraction of EUS and other pelvic floor striated muscles stimulate central inhibitory mechanisms to suppress micturition reflex (inactivation of parasympathetics)

What occurs during micturition?

- storage phase switched to voiding phase either involuntarily (reflex) or voluntarily
 - reflex } infants, neurogenic bladders
 - voluntary } adults
- involves central organization involving spinal & spinobulbospinal pathways through PMC (pons)
- bladder distension to capacity results in stimulation of parasympathetics to bladder and to urethra (mediated by NO)
- bladder distension also results in inhibition of sympathetics & pudendal somatics
- voiding promoted when stimulation of urethra promotes reflex bladder contractions (involves glutamic acid, GABA, and glycine)

How does the urethral-bladder reflex explain mixed incontinence?

- stress leakage into urethra can stimulate afferents and induce detrusor overactivity
 - stress incontinence can induce urge incontinence
- surgical cure of stress incontinence of women with mixed incontinence resolves the urge component in up to 50% of patients

What are the main areas of the BRAIN that are involved during voiding?

- **predominantly by the R side of the brain**
- **frontal lobes**
- **R anterior cingulate gyrus**
- **Pontine Micturition Centre** (dorsomedial pontine tegmentum) } aka Barrington's nucleus
- pre-optic area
- periaqueductal gray
- superomedial frontal lobes and genu of corpus callosum
- right dorsolateral prefrontal cortex
- frontal cortex
- right inferior frontal gyrus
- hypothalamus

What is the role of the pontine micturition centre?

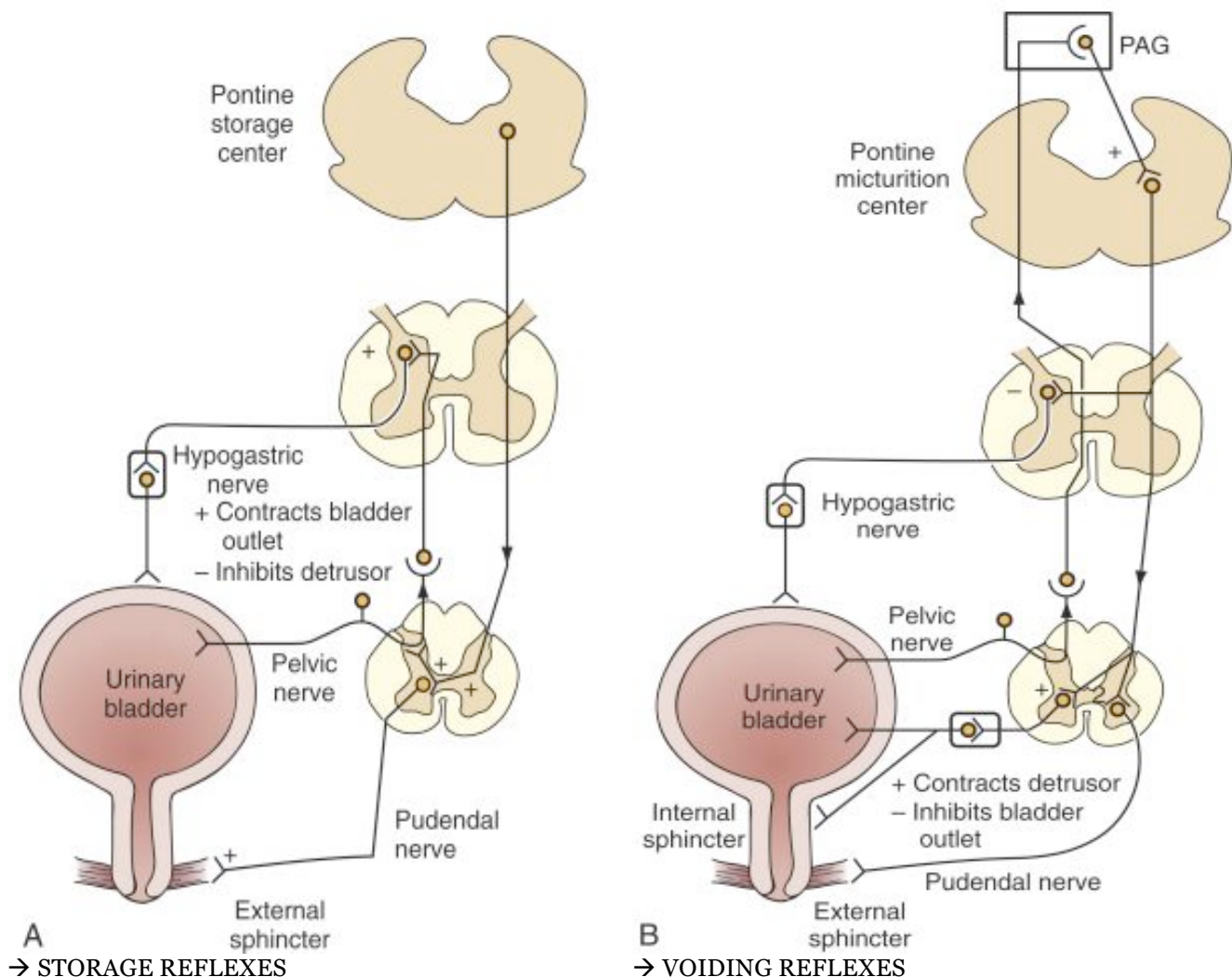
- aka Barrington's nucleus or M region
- **critical for micturition**
- glutamate is major NT
- promotes bladder-sphincter synergy
 - bladder contraction stimulated through sacral preganglionic neurons
 - EUS inhibition mediated through GABAergic neurons in sacral dorsal commissure region
- lesion above colliculus facilitates micturition } elimination of inhibitory inputs
 - } also means can't abort micturition reflex caused by involuntary contractions
 - eg CVA in cerebral cortex or internal capsule
- lesion below colliculi abolishes micturition } elimination of parasympathetics

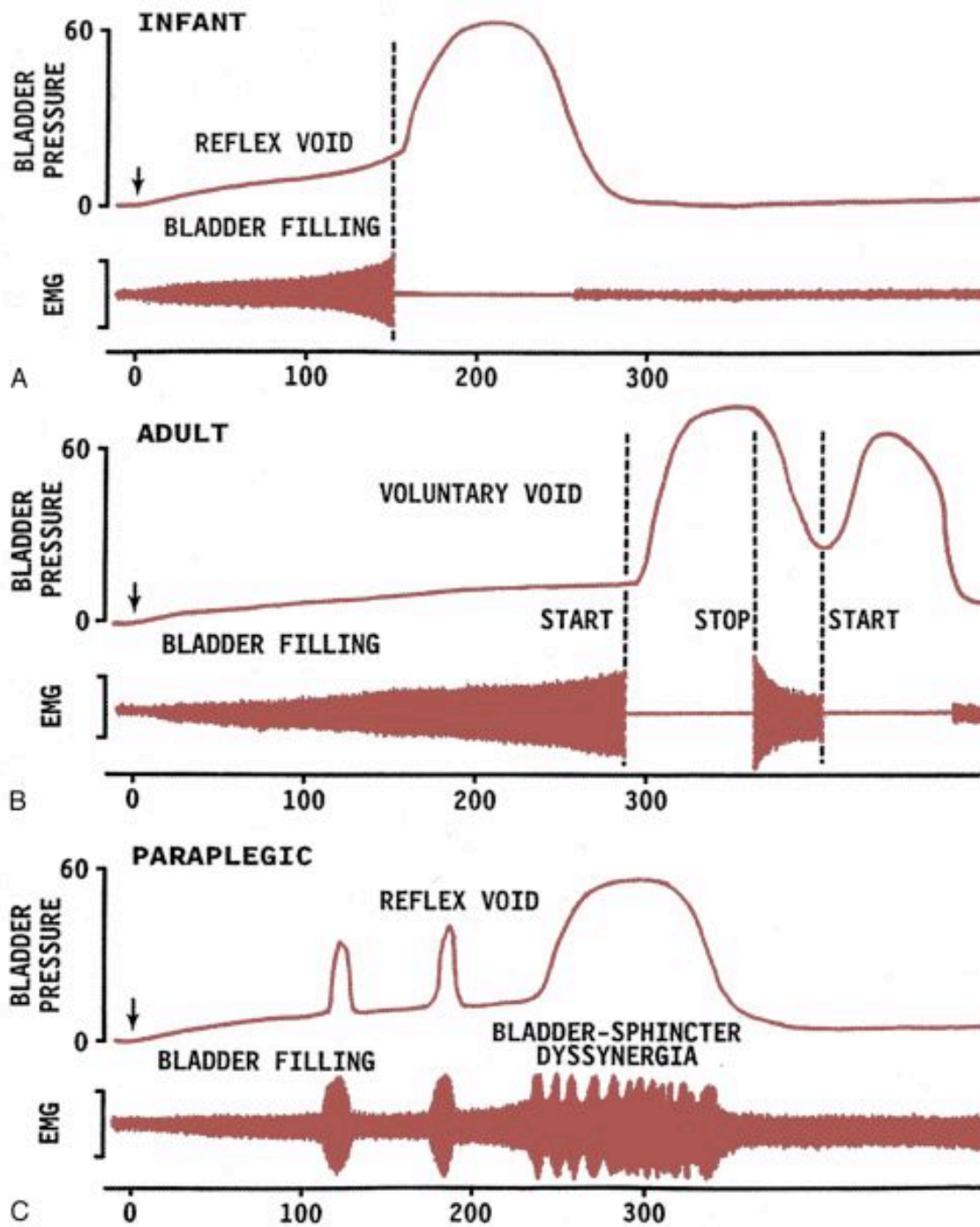
How does sacral neuromodulation work?

- **activation of somatic afferents** that modulate sensory processing & micturition reflex pathways in spinal cord
- 1) retention & dysfunctional voiding
 - spinal guarding reflex } bladder filling stimulates urethral closure
 - sacral stimulation (somatic afferents) **inhibits spinal guarding reflex**
 - bladder filling doesn't stimulate urethral closure
 - stops "DSD" picture & allows voluntary micturition
- 2) detrusor overactivity
 - bladder-bladder reflex } bladder filling sends signal up to brain & PMC tells bladder to empty
 - urethral-bladder reflex } urethral activity stimulates bladder to empty
 - sacral stimulation (somatic afferents) directly inhibits bladder preganglionic neurons, thereby **inhibiting bladder-bladder & urethral-bladder reflexes**

How do neonates develop continence & voluntary voiding?

- **immature bladder reflexively empties when full**
 - infants have OAB
- bladder overactivity neonatal pathways DO NOT disappear with growth and development
- increasing cerebral maturation actively inhibits them
 - neurologic diseases and aging allow neonatal reflexes to re-emerge





→ CMG & EMG DURING VOIDING

PHARMACOLOGY

List drugs that promote bladder storage.

- 1) anti-cholinergics } inhibits muscarinic receptors, reducing cholinergic stimulation effect
→ oxybutynin, tolterodine, atropine, glycopyrrolate
- 2) smooth muscle relaxants } reduces Pves during filling and reduces unstable bladder ctxs
} small degree of anticholinergic action
→ dicyclomine, flavoxate
- 3) CCB } reduces magnitude of spikes during unstable bladder ctxs
→ diltiazem, nifedipine, verapamil
- 4) K⁺ channel openers } increases membrane potential to reduce initiation of unstable ctxs
→ cromakalim, pinacidil
- 5) PG inhibitors } inhibits PG-mediated smooth muscle ctxs
→ flurbiprofen
- 6) β -agonists } induces relaxation of bladder body
→ isoproterenol, terbutaline
- 7) TCAs } anticholinergic effect, direct smooth muscle relaxant effect, NE reuptake inhibition
→ amitriptyline, imipramine
- 8) α -agonists } increases urethral tone
→ ephedrine, phenylpropanolamine, midodrine, pseudoephedrine
- 9) afferent nerve inhibitors } reduces sensory input from bladder, reducing unstable ctxs
→ DMSO, capsaicin, resiniferatoxin
- 10) estrogen } may increase thickness of urothelium, increase urethral blood flow
→ estradiol

How many cholinergic muscarinic receptors are there?

- pharmacologically, bladder contains M1, M2, M3 } but physiologically, M1-M5 have all been found
→ M2 receptors are the most common
→ **M3 receptors mediate bladder contractions**
 - acetylcholine binds to M3 and activates PLC
 - PLC activation leads to IP3 hydrolysis, resulting in the release of Ca²⁺

What is the role of M2 receptors in the bladder?

- **most common receptor but NOT most important**
- coactivation may enhance response to M3 stimulation
 - 1) inhibits adenylate cyclase, suppressing sympathetically mediated depression of detrusor
 - 2) inactivation of K⁺ channels
 - 3) activation of nonspecific cation channels
- M2-mediated bladder contractions **may play larger role in pathologic conditions**

Where in the body are M3 receptors found?

- | | | |
|-----------------------|---|---------------------------------|
| - bladder | \ | |
| - digestive tract | \ | more clinically important to |
| - salivary glands | } | be tissue specific than subtype |
| - pupils | / | selective |
| - reproductive organs | / | |

What is the role of prejunctional muscarinic receptors?

- involved in modulating neurotransmission in bladder
- M1 prejunctional receptor } facilitates acetylcholine release
→ promotes bladder emptying
- M2-M4 prejunctional receptors } inhibits release of acetylcholine
→ suppresses cholinergic contractions during filling

Which pharmacologic agents are involved locally in bladder function?

- | | |
|---|--|
| 1) stimulatory (contractions) | 2) inhibitory (relaxes) |
| - purinergics (P2X, P2Y receptors) | - β -adrenergics (β -3 main receptor) |
| - PDE | - PTH-like peptides |
| - α -adrenergics | - botulinum toxin |
| - tachykinins | - CCB |
| - PGs | - K ⁺ channel openers |
| - endothelins | - TCAs |
| - serotonin | → upregulating these agents could help with OAB |
| - vanilloids (capsaicin) | |
| → blocking these agents could help w/ OAB | |
| → upregulating these agents could help pts w/ atonic bladders | |

What is the role of purinergics in the bladder?

- 2 main families of purinergic receptors } **P2X and P2Y**
 - **plays small role in mechanosensory and nociceptive signaling**
 - may play larger role in pathologic bladders
- predominant expression of P2X1 receptors in bladder
 - increased expression in overactive bladders
- P2X3 receptors also found in bladder
 - involved in sensing bladder distension and initiating contractions

What is the role of β -adrenergics in the bladder?

- β -2 and β -3 adrenergic receptors found in detrusor
- **β -3** adrenoreceptor is main receptor
 - **stimulation results in relaxation of smooth muscle**
 - mediated through adenylate cyclase and cAMP

What is the role of PDE inhibitors in the bladder?

- selective inhibition of bladder PDE would result in increased cAMP & enhanced β -adrenergic effects
 - **PDEIs cause relaxation of bladder**
- specific isoform of PDE in bladder unknown } PDE4 in guinea pig bladders
 - } PDE1 being studied in humans

What is the role of α -adrenergics in the bladder?

- not prominent in normal bladder
- may have larger role in OAB } increased number of α 1D receptor subtype
 - } NE-mediated relaxation converted to contraction

What is the role of α -adrenergics in the urethra?

- plays more prominent role than in bladder
- plays role in urethral tone & intraurethral pressure
 - α 1 receptors more common in M \ α 1 receptors play larger role in urethra
 - α 2 receptors more common in F / tone in both M and F
- α 1A receptor is major subtype in prostate and urethra
 - α 1A, α 1B, and α 1D all present in blood vessels
 - α 1A-specific α -blockers (ie tamsulosin) have less systemic symptoms (eg dizziness, etc)

What is the role of NO in the bladder and urethra?

- mediated mainly via cGMP
- major inhibitory transmitter mediating urethral relaxation during voiding
 - **NO promotes urethral relaxation**
- also involved in controlling bladder afferent nerve activity
 - NOS inhibition results in decreased detrusor overactivity
 - but intravesical NO may suppress detrusor overactivity from cyclophosphamide

List neuropeptides released by noxious stimuli to the bladder.

- non-myelinated, capsaicin-sensitive, C fibers in bladder afferents
- tachykinins } substance P (NK1 receptor)
- } neurokinin A (NK2 receptor), neurokinin B (NK3 receptor)
- calcitonin gene-related peptide (CGRP)
- VIP
- pituitary adenylate cyclase-activating peptide (PACAP)
- enkephalins

What is the role of tachykinins in the bladder?

- involved in bladder afferent input due to noxious stimuli
- NK1 receptors (substance P) } induces plasma extravasation and vasodilation of vessels
- NK2 receptors (neurokinin A) } stimulate bladder contractions
- NK3 receptors (neurokinin B) } increases excitability during bladder filling or during bladder inflammation
- non-nociceptive input mediated via NK1
- nociceptive afferents in bladder mediated by NK1, NK2, NK3

What is the role of PGs in the bladder?

- **involved in bladder contraction** } made primarily in urothelium
→ PGF₂ α most potent
- PGE₂ may induce bladder contractions
→ improved emptying in patients with urinary retention
- inhibition of PG synthesis may decrease detrusor overactivity

What is the role of endothelins in the bladder?

- cause detrusor contractions
- increased expression of ET-1 found in detrusor hyperplasia and overactivity associated with BOO from BPH

What is the role of PTH-related peptide in the bladder?

- helps to promote detrusion relaxation

What is the role of sex steroids in the bladder?

- DO NOT directly affect bladder contractility but they modulate receptors and influence growth of bladder tissues
→ progesterone may increase cholinergic contractions of the bladder
- also affects vasculature and urethra

What is the role of serotonin (5-HT) in the bladder & urethra?

- potentiates bladder contractility } mediated by 5-HT₄ receptor subtype
- increases urethral tone

What is the role of vanilloids (capsaicin, resiniferatoxin) in the bladder?

- stimulates and desensitizes unmyelinated C fibers to produce pain and release neuropeptides
 - C fibers are usually silent } activated by noxious chemical irritants
 - } in pathologic states, they are responsive to low-pressure bladder distension like Aδ fibers
- activate pain sensory nerves via Ca²⁺ channel TRPV1 receptor subtype 1 or VR1
 - excites and subsequently desensitizes C fibers
- **capsaicin predominantly excites**
- **resiniferatoxin predominantly desensitizes**

What is the role of Botulinum toxin in the bladder?

- **7 different toxins } BTX-A to BTX-G**
- consists of light chain and heavy chain
 - prevents release of NT by cleaving SNARE proteins (light-chain mediated)
- acts by inhibiting acetylcholine release at presynaptic nerve terminal
 - inhibits striated and smooth muscle contractions
- may also play a role in reducing NT release from bladder afferents (ATP, substance P, CGRP)
 - may also be good for IC, non-neurogenic bladder overactivity
- may play role in BPH/BOO
 - causes atrophy of prostate

What is the role of CCB in the bladder?

- spontaneous and evoked contractions in bladder are mediated by membrane depolarization and the movement of Ca^{2+} into the smooth muscle via L-type Ca^{2+} channels
 - CCBs may decrease level and severity of spontaneous myogenic contractions
 - CCBs work only on decreasing entrance of extracellular Ca^{2+} , not on intracellular Ca^{2+} from the SR

What is the role of K⁺ channel openers in the bladder?

- 3 different types of K channels
 - ATP-sensitive (KATP), Ca-dependent small conductance (SKCa), and Ca-dependent large conductance (BKCa)
- movement of K⁺ out of the cell results in membrane hyperpolarization and reduced spontaneous contractions
 - upregulating K⁺ channel openers may decrease bladder overactivity

What is the role of TCAs in the bladder?

- have antimuscarinic activity, inhibition of Ca translocation, and direct smooth muscle relaxant properties
→ non-specific agents
- may also have central effect on CNS
→ TCAs relax bladder

How does the urothelium play a role in bladder signaling?

- may play a role in responding to local chemical and mechanical stimuli
 - release chemical signals to bladder afferent nerves
 - NO, ATP, acetylcholine, substance P, PGs
- muscarinic receptors also found in urothelium
 - may play a role in afferent sensory function, not just detrusor contractility

Which pathways are involved in spinal reflex control of the bladder and urethra?

- 1) stimulates contractions/micturition
 - glutamatergic (NMDA, AMPA)
- 2) inhibits contractions/micturition
 - GABAergic (increases threshold for spontaneous contractions)
 - serotonergic (may upregulate EUS activity)
 - opioids
 - purinergics (adenosineA1 receptor)

- adrenergics may be involved in both
 - } excites efferent limb of micturition reflex
 - } inhibits afferent limb of micturition reflex

What is duloxetine?

- blocks serotonin reuptake
- initially recommended for mixed incontinence } relaxes bladder + increases EUS tone
- withdrawn from FDA approval due to suicide risk

Which pathways are involved in central (PMC & supraspinal) control of micturition?

- | | |
|---|--------------------------------------|
| 1) stimulates contractions/micturition | 2) inhibits contractions/micturition |
| - glutamatergic (essential for voiding) | - GABAergic (GABAA & GABAB) |
| - cholinergics | - opioids |
- dopaminergics involved in both } depends on receptor type and site of action in brain
 } stimulatory via D2-D4 and inhibitory via D1 or D5

MECHANISMS OF DETRUSOR OVERACTIVITY

What are the causes of detrusor overactivity?

- Idiopathic
 - Neurogenic
 - Supraspinal lesion
 - stroke
 - Hydrocephalus
 - TBI
 - Suprasacral lesion
 - SCI
 - MS
 - DM
 - Non-Neurogenic
 - BOO
 - bladder stones
 - UTI
 - urethral diverticulum
 - idiopathic
- Parkinson's
 - Brain tumour
 - MS
 - SC tumour
 - spina bifida
 - transverse myelitis
 - post-op
 - bladder tumour
 - DM
 - SUI
 - IC

How do SCIs above the sacral level lead to detrusor overactivity?

- initially get spinal shock } retention x several weeks
- eventually get hyperreflexic voiding
- **new/uninhibited spinal micturition reflexes** develop and lead to detrusor overactivity
 - positive feedback mechanism that may be unresponsive to voluntary control
- **previously silent bladder afferents become more mechanosensitive** to low bladder pressures (C fiber plasticity)
 - activation of unmyelinated C fibers } may also be involved in MS, Parkinson's disease, etc
 - NGF mediates the disease-induced changes in C fibers
 - NGF is made in the hypertrophied bladder and in injured spinal cord

How does BOO lead to detrusor overactivity?

- BOO produces detrusor hypertrophy and changes in smooth muscle cells
 - increased excitability of detrusor
 - increased connexin 43 (gap junction protein)
- BOO also leads to changes in detrusor innervation
 - partial denervation of detrusor
 - supersensitivity to K⁺
- also involves formation of new spinal reflexes
 - hypertrophy of bladder afferent and efferent neurons
 - NGF mediated

How does inflammation lead to detrusor overactivity?

- NGF mediated
- repeated inflammatory stimuli lowers threshold for bladder afferents leading to overactivity
- get increased expression of chemical markers in afferent neurons
 - NOS, protein 43, pituitary adenylate cyclase-activating polypeptide, substance P, PGs, COX-2, protease-activated receptors
- unknown if it involves C fibers

How does age affect bladder contractility?

- no evidence that aging results in diminished contractility
 - bladder muscarinic receptor density is unchanged
 - no differences in detrusor contractile response to cholinergic stimulation
- we do see enhanced adrenergic contractile response in aged bladders
 - might reduce storage capacity and lead to overactivity
- increased PVR & decreased flow rates in elderly may be due to lower energy production
 - not due to decreased NT release } unchanged with aging

What is the key feature found in all pathologic conditions leading to abN voiding?

- neuroplasticity
- nerves supplying lower GU tract can undergo long-term changes that lead to detrusor overactivity
 - increased neurotrophin production (eg NGF)
 - enhanced C fiber afferent evoked bladder reflex
 - noradrenergic function

SUMMARY AND FUTURE RESEARCH

What types of neurologic disease are associated with detrusor overactivity?

- 1) brain } interruption of cortical inhibitory circuits
 - } eg Parkinson's disease, stroke
- 2) spinal cord } damaged pathways from brain to spinal cord
 - } eg MS, SCI
- 3) desensitized bladder afferents } neuroplasticity
 - } eg BOO, IC, DM, aging

Bladder neck – noradrenergic (sympathetic fibers)

Laplace's Law;

$T(\text{tension}) = P(\text{intravesical pressure}) \times R(\text{bladder radius}) / 2d(\text{wall thickness})$

Bladder compliance $c = \Delta v / \Delta \text{pressure}$

$P_{\text{det}} = P_{\text{ves}} - P_{\text{abd}}$

Acetylcholine released from parasympathetic nerves – M3 receptors induce detrusor muscle contractions by calcium entry (thru Ca^{++} channels)

External sphincter (+Rhabdosphincter) – striated (+some smooth muscle)

- Fast twitch + slow twitch (most of the fibers) – slow twitch is constantly firing
- ES = Includes urethral wall=rhabdosphincter and muscles surrounding

Lower Urinary Tract (Peripheral Nerves)

- Parasympathetic S2 – 4, excite the bladder +relax urethra
- Sympathetic – lumbar, inhibit bladder body, excite the bladder base+ urethra
- Somatic – Pudendal excite the external urethral sphincter

Parasymp – S2 –S4 –preganglionic – Acetylcholine

-postganglionic in bladder wall (intramural ganglia)

T10 – L2 – Sympathetic chain ganglia – inferior Mesenteric ganglia – hypogastric nerves – pelvic ganglia

Somatic – external urethral sphincter motorneurons are located along the lateral border of the ventral horn – commonly referred to as Onuf's nucleus

During neuropathic conditions and possibly inflammatory conditions – there is recruitment of C-fibers (mechanosensitive) that form a new functional pathway

Afferent Pathways – sense bladder volume (c-fibers are part of this)

Storage Phase and Micturition/Expulsion Phase:

PMC – in brainstem (at the level of the inferior colliculus)

Voluntary control of voiding – frontal cortex and anterior cingulate gyrus (predominantly by right side of brain)

- Maturational control

Sacral Neuromodulation depends on electrical Stimulation of afferent axons in the spinal roots that in turn modulate voiding and continence reflex pathways in the CNS

Muscarinic Receptors – 5 subtypes

M1, M2, M3 found in bladder wall

M2 more predominate but M3 mediate cholinergic contractions

B adrenergic (B2 + B3) in bladder wall can result in direct relaxation of the detrusor muscle.

Capsacin (Vanilloids) – Stimulate and desensitize a specific population of sensory nerves (unmyelinated C- Fibers) to produce pain and release neuropeptides

- Painful to instill into bladder, need to anesthetize

Botox – acts by inhibiting acetylcholine release at the presynaptic cholinergic nerve terminal, thereby inhibiting striated and smooth muscle contractions.

Duloxetine – a combined norepinephrine and 5-HT reuptake inhibitor – has been shown to increase neural activity of both the urethral sphincter and bladder (used only in Europe for SUI)

Classification of Voiding Dysfunction

Functional

Failure to store

- bladder
- urethra

Failure to empty

- bladder
- urethra

Urodynamic Classification

Lapides Classification

Bors –Comarr (unbalanced)

Hald-Bradley

Bradley (loop system)

Urodynamics

Principles:

1. A study that does not duplicate patient's symptoms is not diagnostic
2. Failure to record an abnormality is not diagnostic (20-30 UDS miss OAB)
3. Not all abnormalities detected are clinically significant

Aim of Urodynamics studies is to reproduce symptoms while making precise measurements of the bladder physiology. You need an expert present while performing.

Indications:

Perform the study if you feel you can gain important information that will assist you in the diagnosis and treatment of a patient

Neuro-urology Power Summary

Pre testing

1. Need for antibiotics (controversial)
 - a. Consider with indwelling foley/recurrent UTIs
 - b. Post UDS: prosthetics
2. Stop bladder and prostate medications
3. Voiding diary

Measurements

Rectal Pressure = Pabd cmH₂O

Pdet – Subtracted “true” bladder pressure cmH₂O

Infusion rate cc/min → too fast = OAB stimulation, poor compliance artifactually and not physiological

Volume infused cc

Flow rate cc/sec

Voided Volume cc

EMG (needles –more accurate or patches)

(Urethral Pressure measurement)

Uroflow – should be a continuous, bell-shaped curve with rapidly increasing flow rate

- Insufficient to diagnose BOO – low flow may be due to obstruction, vs. weak detrusor
- max flow, time to void, volume voided (needs to be >150cc)

Uroflow in males Q max >15 ml/sec goes down with age

Uroflow in women. Q max can be >30ml/sec. Flow time shorter, not age dependent

CMG

Zero pressure – surrounding atmospheric pressure outside at level of bladder

Reference point/height is the superior edge of the pubic symphysis

Gas – compressible, not physiologic, cannot detect leakage, hard to assess volumes, cannot do voiding studies

Temperature of Fluids – should be at near body temps

Fill rate – slow, medium, rapid

Filling – capacity, sensation, compliance + OAB

Maximum cystometric capacity – end of filling with patient having a strong desire to void

- Cannot delay voiding

Functional bladder capacity – largest volume voided on voiding diary

Sensations

– first sensation

-first desire to void

- strong desire to void

Compliance = ml/cm H₂O, **should be greater than 12.5ml/cm H₂O**

OA – previously called bladder instability

->15cm H₂O but reference has changed ; now just needs to look like bladder contraction

- idiopathic (non-neurogenic) vs. neurogenic OA

Detrusor pressure at maximal flow

Neuro-urology Power Summary

Maximum detrusor pressure regardless of flow

PVR – absence of does not mean no obstruction

Pressure Flow – nomogram

- Males > 40 cmH₂O obstructed?
- Female's > 25-30 cmH₂O obstructed?

Video UDS – most accurate

- Visualize location of obstruction
- Reflux, diverticuli, cystocele, descensus, urethra, bladder neck obstruction. Fistula BPH, PVR, Stress testing, etc
- Standing and sitting (can miss OAB if lying)
- Why not flat?

EMG – to assess co-ordination of external sphincter and bladder

DSD vs. Pelvic Floor hyperactivity

- DSD is a neurological finding
- PFH

Parkinson's disease – sphincter bradykinesia – delay in relaxation of sphincter with voiding due to skeletal muscle hyperactivity

Detrusor Leak Point Pressure (lowest pressure to overcome urethral resistance)

- For SUI
-

Abdominal Leak Point Pressure – ISD

UPP – urethral pressure profile

Neurogenic Voiding Dysfunction

Table 59-1 page 2012 – excellent summary

General Principles

Lesion above the brain stem

- involuntary bladder contractions
- Coordinated sphincter function
- Sensation usually okay or may be deficient or delayed
- Detrusor areflexia may occur initially or permanently

Lesions T6 –S2 (b/w symph outflow and sacral cord)

- OA
- No sensation
- Smooth sphincter synergy
- Striated sphincter dyssynergia
- Lesions between brain stem + T6 – may have smooth sphincter dyssnergia + autonomic hyperreflexia
- In both can get retention
- Can get decrease compliance

Neuro-urology Power Summary

Lesions below S2

- No OA
- Detrusor Areflexia, possible decreased compliance
- Open smooth sphincter
- No real striated sphincter dyssynergia but a fixed resting tone

CVA – Initially retention due to detrusor areflexia (cerebral shock)

- Eventually OA

Dementia – incontinence

- Cause - lack of awareness
- Aricept type drugs- concern → May cause worsening of OAB (no evidence)

Traumatic Brain Injury – location of injury

- Initial detrusor areflexia

Brain Tumor – location of tumor

- OA usually

Cerebellar Ataxia

- OA
- Sphincter synergy
- Possible detrusor areflexia + DSD can occur if spinal cord is involved

NPH – usually OA

- Sphincter synergy

Cerebral Palsy – usually normal bladder dysfunction

- If incontinence usually OA + sphincter synergy
- If severe hypoxia at birth + severe cerebral palsy – OA +DSD

Parkinson's – 35 -70% have voiding dysfunction

- Urgency, frequency, nocturia + urge incontinence
- OA, smooth sphincter synergy
- Pseudodyssnergia, bradykinesia
- Areflexia uncommon

MSA – multisystem atrophy– progressive neurodegenerative disease (Shy-Drager)

- Bladder symptoms occur earlier than PD and more severe and ED occurs
- Orthostatic hypotension (cannot use alpha-blockers, esp non specific ones), anhidrosis, PD and cerebellar dysfunction
- OA, urge leakage, PVR
- May get decreased compliance
- Open bladder neck, striated sphincter denervation
- Impaired contractility

Neuro-urology Power Summary

MS

- 50-90% complain of voiding dysfunction
- Incontinence 37-72%
- OA most common (34-99%)
- DSD 30-65%
- Impaired contractility or areflexia 12-38%
- Rarely causes upper tract damage

SCI – cord vs. column level

- Sacral spinal cord begins at T12 – L1 column level, the cord terminates at the cauda equina at spinal column level L2

Spinal Shock – Flaccid bladder

- BN closed
- Weeks to months

Lesions above Sacral Cord but below sympathetic outflow

- OA, smooth sphincter synergy + DSD
- Weak, absent or poorly sustained bladder contraction
- Tx – CIC + anticholinergics, monitor upper tracts (+sphincterotomy)

Sacral Spinal Cord Injury

- Detrusor Areflexia with high or normal compliance
- Competent but non-relaxing smooth sphincter and a striated sphincter that retains some fixed tone but is not under voluntary control

Level of neurological injury (complete or partial) does not always correlate with urodynamics findings especially with injuries at T10 – L2 spinal column

Autonomic Hyperreflex (dysreflexia)- represents an acute massive disordered autonomic (primarily sympathetic) response to specific stimuli in patients with SCI above the cord level of T6 to T8 (the sympathetic outflow)

- Headache, HTN, flushing of the face and body above the level of the lesion with sweating
- Bradycardia (although can have tachycardia or arrhythmia)
- Stimuli usually from bladder or rectum (DSD + smooth sphincter dyssnergia)
- Premedicate on Hytrin/alpha blocker or nifedipine (SL)

Reflux – treat elevated bladder pressures

UTI – treat bacteria when symptomatic

Follow-up of SCI

- Yearly imaging (U/S)
- Cysto if indwelling catheter
- Urodynamics as needed

Neuro-urology Power Summary

Spina Bifida – Myelomeningocele

- “typical “ – areflexic, open bladder neck, fixed external sphincter (can result in stress leakage)
- Some have DSD
- Cannot predict what the urodynamics will show by level of lesion

Tethered Cord Syndrome (TCS)

- spina bifida children as they grow
- Or adults (spina bifida occulta)

Disk disease or prolapsed

- most disk protrusions compress the spinal roots in the L4-L5 or L5 –S1 vertebral interspaces
- Normally compliant areflexic bladder
- Numbness/sensory loss in the perineum or perianal area (S2-S4 dermatomes)
- Cauda Equina Syndrome – disk protrusion or spinal canal pathology – perineal sensory loss, loss of voluntary control of both anal and urethral sphincter

Radical Pelvic Surgery – radical hysterectomy, Abdominoperineal resection, etc

- Areflexic or impaired contractility, obstruction with a fixed striated sphincter tone (not under voluntary control)
- Smooth sphincter is open and non-functional
- Decreased compliance
- Increased risk of upper tract deterioration

Diabetes – peripheral and autonomic neuropathy affects sensory afferent pathways (decreased bladder sensation)

- Overstretching of detrusor and muscle dysfunction

Chapter #57 – Voiding Dysfunction

NORMAL LOWER URINARY TRACT FUNCTION: OVERVIEW

What are the 2 phases of the normal micturition cycle?

- 1) bladder filling & urine storage
 - **N compliance** (↑'ing urine volumes + low intravesical pressure) & **appropriate sensation**
 - bladder outlet that's closed at rest & remains so during ↑'d intra-abdominal pressures
 - absence of detrusor overactivity
- 2) bladder emptying or voiding
 - **coordinated contraction** of bladder smooth muscle of adequate **magnitude & duration**
 - concomitant lowering of resistance at level of smooth and striated sphincter
 - absence of anatomic obstruction

MECHANISMS UNDERLYING THE 2 PHASES OF FUNCTION: OVERVIEW THE MICTURITION CYCLE: SIMPLIFICATION AND OVERVIEW

What allows for normal bladder filling?

- at physiologic fill rates, there is essentially no rise in bladder pressure until bladder capacity is reached
- slight rise in pressure during CMG is due to fill rate being > physiologic
- 1) anatomic factors } relaxed detrusor smooth muscle
 - } elasticity of bladder wall constituents
 - } viscoelastic properties of mainly stroma (collagen, elastin)
 - poor compliance associated with ↑'d collagen
- 2) reflexes } lack of parasympathetic excitatory input
 - } spinal sympathetic reflexes allow for bladder filling/storage
 - mediated by sympathetic modulation of cholinergic signals
 - stimulation of β-adrenergics in bladder } inhibits contractions
 - stimulation of α-adrenergics in internal sphincter } ↑'d outlet tone
 - } other reflexes that promote normal bladder filling
 - guarding reflex } gradual increase in EUS activity during N bladder filling/storage
- 3) other } tonic inhibitory effect of other neurotransmitters eg opioids
 - } complex supraspinal inputs that inhibit normal micturition

What allows for normal voiding?

- Pves producing sensation of distension is primarily responsible for initiation of N voluntary voiding
- coordinating centre for micturition reflex is PMC
- 1) anatomic factors } absence of anatomic obstruction distal to bladder
- 2) reflexes } activation of parasympathetic neural outflow from sacral spinal cord via pelvic nerves
 - bladder contraction + EUS relaxation } involves shaping or funneling of relaxed outlet
 - } inhibition of continence-promoting reflexes
 - eg spinal sympathetic reflexes, guarding reflex
 - } other reflexes that reinforce complete bladder emptying
 - eg urethral-bladder reflex
- 3) other } active relaxation of internal smooth sphincter
 - occurs via NANC mechanism (mediated by NO)
 - } complex supraspinal inputs that promote normal micturition

Why is there normally no leakage of urine with increased intra-abdominal pressure?

→ **continence is never compromised with Valsalva maneuvers in N system (no N VLPP)**

- 1) intrinsic competence of bladder outlet
- 2) intra-abdominal pressure is equally transmitted to proximal urethra } increases closure pressures
- 3) reflex ↑ in striated sphincter activity } active muscular function to ↑ urethral closure pressure by more than ↑ in intra-abdominal pressure

ABNORMALITIES OF FILLING/STORAGE AND EMPTYING/VOIDING: OVERVIEW

What are the abnormalities of bladder filling/urine storage?

- 1) bladder overactivity
 - involuntary contractions } most commonly seen w/ neurologic injury/disease
 - } can also be d.t. inflammation or irritation that result in ↑'d afferent input
 - low compliance } usually due to neurologic injury/disease at or below sacral level
 - } can also be d.t. process that destroys viscoelastic/elastic properties of wall
 - some combination of the above
- 2) decreased outlet resistance
 - from any process that damages innervation or structure of smooth or striated sphincter or from damage to support of the bladder outlet in females
 - neurologic injury/disease, surgical or mechanical trauma, aging
- 3) heightened or altered sensation
- 4) some combination of the above

What are the causes of involuntary contractions of the bladder?

- idiopathic
- neurologic disease or injury
- inflammation or irritation of bladder or urethral wall (↑d afferent input)
- BOO
- SUI
- aging (?neural degeneration)

What are the causes of sphincteric incontinence in females?

- 1) "genuine stress incontinence"
 - urethral/BN hypermobility } due to a lack of stability of suburethral supports
 - never the sole cause of stress incontinence } can be present in continent women
- 2) intrinsic sphincteric deficiency (ISD)
 - present in all cases of SUI } usually due to prior Sx, trauma + scarring, or a neurologic lesion
 - stress incontinence in men is related to ISD

What are the abnormalities of bladder emptying/voiding?

- 1) decreased bladder contractility
 - from temporary or permanent change in neuromuscular mechanism necessary for initiating & maintaining N detrusor contractions
- 2) increased outlet resistance
 - outlet overactivity or BOO } DESD common cause of obstruction in pts w/ neurologic injury/disease
 - much more common in M
- 3) some combination of the above

What are the causes of poor bladder contractility?

- neurologic disease or injury (eg APR, DM)
- impaired bladder smooth muscle function (eg overdistension)
- centrally or peripherally acting drugs
- severe infection
- fibrosis

CLASSIFICATION SYSTEMS

What are the features of an ideal classification system for voiding dysfunction?

- based on conclusions from urodynamic testing
- expected clinical symptoms
- approximate site and type of neurologic lesion, or lack of one
- obvious treatment options for each

What is the functional classification of voiding dysfunction?

- 1) failure to store
 - bladder problem } involuntary contractions
 - } low compliance
 - } heightened or altered sensation
 - outlet problem } decrease in outlet resistance (ISD, hypermobility)
- 2) failure to empty
 - bladder problem } poor bladder contractility (neurogenic, myogenic, idiopathic)
 - outlet problem } obstruction or sphincter overactivity

What are the treatment options to improve bladder STORAGE?

- 1) **bladder problem } inhibiting ctx's, ↓'ing sensory input, ↑'ing capacity**
 - behaviour therapy } bladder training, education, habit changes, voiding diary
 - pelvic floor muscle training +/- biofeedback
 - meds } anticholinergics } α-blockers
 - } drugs with mixed action } TCAs
 - } CCBs } DMSO
 - } K+ channel openers } polysynaptic inhibitors
 - } PG inhibitors } capsaicin, resiniferatoxins (vanilloids)
 - } β-agonists } botox
 - electrical stimulation or neuromodulation
 - acupuncture/electroacupuncture
 - interruption of innervation } subarachnoid block, sacral rhizotomy, peripheral
 - surgery } hydrodistension, augmentation cystoplasty (auto, bowel, bioengineering)
- 2) **outlet problem } ↑'ing resistance**
 - behaviour therapy } bladder training, education, habit changes, voiding diary
 - pelvic floor muscle training +/- biofeedback
 - electrical stimulation
 - meds } α-agonists (pseudoephedrine)
 - } TCAs
 - } β-blockers
 - vaginal/perineal occlusive or supportive devices
 - non-surgical periurethral bulking } collagen, synthetics, cell transfer
 - surgery } vesicourethral suspensions, slings, AUS, closure of bladder outlet, bladder outlet reconstruction, myoplasty (muscle transposition)
- 3) **symptomatic management only**
 - pads, anti-diuretics, CIC, continuous catheterization, urinary diversion

What are the treatment options to improve bladder EMPTYING (CHART)?

1) bladder problem } ↑ intravesical pressure or ↑ bladder contractility

- external compression, valsalva
- promotion or initiating of reflex contraction } trigger zones/maneuvers
- } bladder “training”
- meds } parasympathomimetics (eg bethanechol)
- } PGs
- } α-blockers
- } opioid antagonists
- electrical stimulation } bladder or SC, nerve roots, intravesical, neuromodulation
- surgery } reduction cystoplasty
- } bladder myoplasty (muscle wrap)

2) outlet problem } ↓ resistance

- at site of anatomic obstruction } meds (α -blockers, 5ARIs, LHRH agonist/antagonist,
anti-androgens)
- } surgery (TURP, prostatectomy, TUIBN, urethral dilation,
urethroplasty, urethral stent)
- at level of smooth sphincter } meds (α -blockers, β -agonists)
- } surgery (TUR or TUI, Y-V plasty)
- at level of striated sphincter } behaviour therapy +/- biofeedback
- } meds (benzos, baclofen, dantrolene, α -blockers, botox)
- } surgery (urethral overdilation, sphincterotomY, stent,
pudendal nerve ablation)

3) symptom management only

- CIC
- continuous catheterization
- urinary diversion (conduit)

What are the features of UDS as they relate to bladder filling & emptying (CHART)?

	Bladder	Outlet
Filling/Storage	<ul style="list-style-type: none"> - Pves during filling - Pdet during filling - filling CMG - DLPP 	<ul style="list-style-type: none"> - UPP - VLPP - fluoroscopy
Emptying	<ul style="list-style-type: none"> - Pves during voiding - Pdet during voiding - voiding CMG 	<ul style="list-style-type: none"> - MUPP - EMG - fluoroscopy

What is the International Continence Society (ICS) Classification of voiding dysfunction?

→ based on UDS findings

→ detrusor overactivity = “involuntary detrusor contractions during the filling phase which may be spontaneous or provoked”

- 1) storage phase
 - bladder function } detrusor activity
 - normal or stable
 - overactive } neurogenic
 - } idiopathic (non-neurogenic + “NYD”)
 - } bladder sensation
 - normal
 - increased or hypersensitive
 - reduced or hyposensitive
 - absent
 - } bladder capacity
 - normal
 - high
 - low
 - urethral function } normal closure
 - } incompetent closure
- 2) voiding phase
 - bladder function } detrusor activity
 - normal
 - underactive
 - acontractile
 - areflexic
 - urethral function } normal
 - } abnormal
 - mechanical obstruction
 - overactivity
 - dysfunctional voiding
 - DSD
 - non-relaxing urethral sphincter dysfunction

→ detrusor hyperreflexia now called **NEUROGENIC DETRUSOR OVERACTIVITY**

→ detrusor instability now called **IDIOPATHIC DETRUSOR OVERACTIVITY**

→ bladder capacity & compliance are cystometric measurements

What is the **UDS classification** of voiding dysfunction?

→ based solely on **objective urodynamic data**

- 1) neurogenic detrusor overactivity (hyperreflexia or normoreflexia)
 - coordinated sphincters
 - striated sphincter dyssnergia (common after complete SCI above sacral level)
 - smooth sphincter dyssnergia (most commonly seen in autonomic hyperreflexia)
 - non-relaxing smooth sphincter
- 2) detrusor areflexia
 - coordinated sphincters
 - non-relaxing striated sphincter
 - denervated striated sphincter
 - non-relaxing smooth sphincter

What are the disadvantages of the urodynamic classification of voiding dysfunction?

- difficult to use when detrusor areflexia is present
- only works if there is total agreement on urodynamic findings
- no mention of compliance, sensation, or deficient but not absent detrusor contractile function

What is the **Lapides Classification system** of voiding dysfunction?

→ includes **clinical & urodynamic status**

- 1) sensory neurogenic bladder } loss of sensory fibers b/w bladder and SC or afferents to brain
 - DM, tabes dorsalis, pernicious anemia
 - impaired sensation of bladder distension
 - large capacity, high compliance, low pressure filling
- 2) motor paralytic bladder (motor neurogenic bladder) } destruction of parasympathetic innervation of bladder
 - extensive pelvic surgery, trauma
 - painful retention or only relative inability to initiate and maintain normal micturition
 - absent voluntary bladder contractions at capacity
- 3) uninhibited neurogenic bladder
 - LUTS, normal sensation, involuntary contractions at low volumes
 - CVA, brain tumour, SC tumour, Parkinson's disease, MS
- 4) reflex neurogenic bladder } complete interruption of sensory & motor pathways between sacral SC & brain stem
 - like complete UMN lesion } describes post-spinal shock condition
 - traumatic SCI, transverse myelitis, extensive demyelinating disease
 - no bladder sensation, inability to initiate voluntary voiding, low-volume involuntary ctx's
 - all get striated sphincter dyssnergia
- 5) autonomous neurogenic bladder } complete sensory & motor separation of bladder from sacral SC
 - any disease that destroys sacral SC or causes extensive damage to sacral roots or pelvic nerves
 - like complete LMN lesion
 - inability to initiate voluntary micturition, no bladder reflex activity, no bladder sensation
 - may develop decreased compliance

What is the **Bors-Comarr Classification** of voiding dysfunction?

→ **only applies to patients with neurologic dysfunction**

→ considers 3 factors } anatomic localization of lesion
 } neurologic completeness or incompleteness of lesion
 } whether lower urinary tract function is balanced or unbalanced
 → >20% PVR in patient with UMN lesion is unbalanced
 → >10% PVR in patient with LMN lesion is unbalanced

- 1) sensory neuron lesion
 - incomplete, balanced
 - complete, balanced
- 2) motor neuron lesion
 - balanced
 - imbalanced
- 3) sensory-motor neuron lesion
 - UMN lesion \ complete, balanced
 - / complete, imbalanced
 - LMN lesions / incomplete, balanced
 - \ incomplete, imbalanced
 - mixed lesion } upper somatomotor neuron, lower visceromotor neuron
 - } lower somatomotor neuron, upper visceromotor neuron
 - } normal somatomotor neuron, lower visceromotor neuron

What are the disadvantages of the Bors-Comarr classification system?

- erroneously assumes sacral SC is primary reflex center for micturition
- UMN bladder = suprasacral SCI
- LMN bladder = injury to sacral SC or sacral roots
- only applies to patients with neurologic dysfunction
- difficult to apply to multicentric neurologic disease
- doesn't make room for variations in clinical and urodynamic findings
- neuroplastic changes can occur that make predicting lower urinary tract features solely on the basis of neurologic lesion almost impossible

What is the Hald-Bradley Classification system for voiding dysfunction?

- 1) suprasacral lesion } overactivity + synergy + normal sensation
 } may get detrusor areflexia and defective sensation
- 2) suprasacral spinal lesion } UMN lesion
- 3) infrasacral lesion } LMN lesion
- 4) peripheral autonomic neuropathy } deficient sensation + gradually rising PVR
 } ultimately get loss of contractility
- 5) muscular lesion } can involve detrusor, smooth sphincter, or striated sphincter

What are the disadvantages of the Hald-Bradley classification system?

→ TOO CONFUSING

What is the **Bradley Classification** of voiding dysfunction?

→ based primarily on neurologic system

- 1) loop 1 } involuntary bladder contractions
 → brain tumour, CVA, cerebral atrophy with dementia
- 2) loop 2 } detrusor areflexia + retention acutely
 } involuntary bladder contractions chronically
 → SCI
- 3) loop 3 } DSD or involuntary sphincter relaxation
 → bladder afferents and pudendal efferents
- 4) loop 4 } DSD or loss of ability to voluntarily contract striated sphincter
 → loop 4a and 4b
 → suprasacral afferents & efferents, periurethral striated afferents, pudendal nerves,
 Onuf's nucleus

What are the disadvantages of the Bradley classification system?

- only applicable for neurogenic voiding dysfunction
- hard to describe multicentric or partial lesions
- can't test intactness of each loop on urodynamics

Chapter #58 – Urodynamics and VUDS

INDICATIONS

What is the goal of UDS?

- **to answer specific questions related to storage & voiding function of the patient's lower urinary tract**
- important to reproduce pt's presenting symptoms & make precise measurements of bladder physiology
- 1) a study that does not duplicate the patient's symptoms is not diagnostic
- 2) failure to record an abnormality does not rule out its existence
- 3) not all abnormalities detected are clinically significant

What are the indications for UDS (CHART – unorganized list)?

- planned or failed therapy
 - **incontinence + mix of stress & urge symptoms**
 - LUTS suggestive of **BOO**
 - LUTS with **both obstructive + marked irritative symptoms**
 - **potential therapy for LUTS** may have significant side effects
 - **persistent LUTS** despite presumed appropriate therapy
 - **recurrent incontinence** in patient **planned for surgery**
- neurologic disease (eg MS, Parkinson's, SCI, etc)
 - **all neurologically impaired patients with neurogenic bladder dysfunction**
 - neurologic disorders with a **mismatch between symptoms & clinical findings**
 - **neurologic disease + obstructive LUTS**
 - **neurologic disease + incontinence**
- paed's
 - **young men with LUTS**
 - kids with **daytime urgency + urgency incontinence**
 - kids with **persistent diurnal enuresis**
 - kids with **spinal dysraphism**

List indications for UDS. } } } “CRRYPT My Neurogenic Bladder”

Combined storage & voiding symptoms
 Refractory to presumed appropriate Rx
 Recurrent Incontinence in pt planned for Sx
 Young men with LUTS
 Paeds } Daytime urgency, Diurnal enuresis persists, Dysraphism
 Therapy planned
 Mixed incontinence (stress & urge)
 Neurologic patient
 BOO

PREPARATION OF PATIENTS

What are the potential complications of UDS?

- AUR
- hematuria
- UTI/pyelonephritis
- pain

What is involved in preparing a patient for UDS?

- 1) complete Hx and P/E
 - fully characterize LUTS
 - questionnaires } IPSS
 - } voiding diary – determine fxn'l capacity, daily u/o & approximate fill volume
 - PMHx, meds, allergies
 - treatment to date
 - neuro exam
 - abdo, GU and pelvic exam
- 2) counseling patient on goals & risks prior to study
- 3) stop all therapeutic meds } α-blockers, anticholinergics, psychotropic meds, etc
 - some don't advocate this (eg Herschorn)
- 4) quiet, clean, private location, minimal staff to facilitate relaxed patient
- 5) treat all active infections FIRST
- 6) prophylactic Abx } YES for ONLY HIGH RISK patients
 - ie previous IE, prosthetic valve, congenital heart disease, etc
 - ie joint prostheses placed <2yrs ago, hx of prosthetic infection,
 - immunocompromised, significant illnesses (DM, malignancy,
 - malnourishment, etc), indwelling catheters/stents, etc
 - } NO for any pins, plates, or screws, and pacemakers
- 7) watch for autonomic dysreflexia } SCI above T6

URODYNAMIC EQUIPMENT

What are the minimum requirements for the equipment used to conduct UDS?

- recommendations made by International Continence Society (ICS)
- 3 measurement channels } 2 for pressure and 1 for flow
- display } monitor or printer
- method for secure storage of recorded pressures (abdo, vesicle, detrusor) and flow measurements as tracings against time
- recording (graphically or numerically) of infused and voided volumes
- method for event (sensation, leakage, etc) recording during study

What measurements should be displayed over time according to ICS standards for UDS?

- 1) Pabdo
 - 2) Pves
 - 3) Pdet
 - 4) flow (Q)
- filling volumes, EMG, and voided volumes can also be displayed

How is pressure measured?

- pressure transducer } converts applied pressure into electrical signal
- 1) open-ended catheter
- 2) sealed catheter filled with liquid or gas (less variability)
- 3) directly via microtip transducer

Table 58-2 -- The International Continence Society Minimal Standards

Accuracy:	±1 cm H ₂ O for pressure
	±5% of the full scale for flow
Detection ranges:	0 to 250 cm H ₂ O for pressure
	0 to 50 mL/sec for flow
	0 to 1000 mL for volume
Time constant:	0.75 seconds
Software:	No loss of data for pressures up to 250 cm H ₂ O and flow up to 50 mL/sec
Frequency:	Analog/digital frequency of 10Hz per channel
	20 kHz minimum may be needed for EMG
Printout:	Line resolution better than 0.10 mm
Maximum deflection:	
Pressure:	200 cm H ₂ O
Flow:	50 mL/sec
Volume:	1000 mL
Minimum scaling:	
Pressure:	50 cm H ₂ O per cm
Flow:	10 mL/sec per cm
Time axis:	1 min/cm or 5 sec/mm for filling
	2 sec/mm for voiding

What are the 4 basic types of pressure transducers used for cystometry? } } } “RICO”

- 1) Resistive
 - 2) Inductive
 - 3) Capacitive
 - 4) Optoelectronic
- pressure measured in cm H₂O
→ **transducer normally calibrated against Patm with zero reference level being superior edge of pubic symphysis**

What are the common UDS equations used (CHART)?

- 1) Flow rate (mL/sec)
 $Q = dV/dt$
- 2) compliance (mL/cm H₂O)
 $C = dV/dP_{det}$ } P_{det} at max cystometric capacity vs P_{det} at start of filling
- 3) detrusor pressure (cm H₂O)
 $P_{det} = P_{ves} - P_{abd}$
- 4) physiologic filling rate for cystometry (mL/min)
Physiologic fill rate = body weight (kg)/4

What are the usual catheters used for normal UDS?

- urethra
- a) 2 catheter technique } 10Fr filling catheter “piggy-backed” with 4Fr pressure catheter
} 10Fr catheter can be removed after filling and cystometry
 - b) double lumen catheter } allows for filling and bladder pressure measurement
} 6Fr is smallest available
 - c) triple lumen catheter } allows for filling, intravesical pressure measurement & urethral pressure recording
- rectal/vaginal
- balloon catheter is best } air-free balloon w/ small fluid volume at catheter opening to avoid fecal blockage which prevents pressure transmission

What are the 3 different types of flowmeters used for uroflowmetry?

→ most calibrated for H₂O, so variations in density of fluid may significantly affect flow rate
eg contrast is more dense than water and may result in overestimation of flow rate

- 1) gravimetric } measures weight over time
- 2) rotating disk } measures flow rate by calculating power required to keep disk rotating
at a constant rate when flow directed onto disk
- 3) electronic dip stick } measures volume over time, indirectly, by recording electrical
capacitance of a dipstick in collecting chamber

What are the 5 different types of electrodes used for EMG?

→ measures depolarization of muscle membranes

- 1) adhesive skin patch } mainly for kids
 } non-invasive and allows for mobility
 } least accurate for underlying muscle
- 2) needle } restricts mobility and invasive
 } more accurate recordings with better specificity for muscle groups
- 3) wire } stainless steel, copper, or platinum placed via needle cannula (invasive)
 } more mobility because can be secured and more accurate with specific recordings
- 4) monopolar } thin needle coated with insulating material except at tip (invasive)
 } need reference electrode (small metal disk on skin near muscle)
 } provides excellent recordings of very specific muscles
- 5) concentric } wire inside outer cannula, separated by insulating material (invasive)
 } can record from 1 to 3 motor units simultaneously

CONDUCTING THE URODYNAMIC EVALUATION

What are the 2 main methods of UDS?

- conventional UDS } artificial filling
- ambulatory UDS } natural filling + reproduction of everyday activities

What are the different UDS components available for evaluating storage & voiding function?

→ storage

- **CMG (+ LPPs)**
- bethanechol supersensitivity tests
- ice water test
- UPP

→ voiding

- **uroflowmetry + PVR**
- **pressure-flow studies**
- **video UDS**
- EMG

Uroflowmetry

What important data is obtained from uroflowmetry?

- Qmax
 - total voided volume
 - avg flow rate + pattern
 - PVR
- \ **only valid with voided**
/ **volumes ≥ 150cc**
/

What are the different patterns of flow seen on uroflowmetry?

- 1) normal } continuous, bell-shaped, smooth curve with rapidly increasing flow rate
- 2) obstructed } plateau-shaped curve with a prolonged flow time, sustained low flow rate, and increased time to Qmax (eg BOO, strictures)
→ BPH more smooth, strictures more of a flat plateau
- 3) intermittent } several episodes of flow increasing or decreasing (or ceasing completely)
} commonly due to abdo straining or external sphincter spasm (eg DSD)

→ uroflowmetry can't accurately distinguish obstruction from poor detrusor contractility

What are the “normal values” on uroflowmetry?

→ no gold standard reference values

→ men

- “normal” } Qmax >15-20 cc/sec
- “abnormal” } Qmax <10 cc/sec
- equivocal zone } 10-15 cc/sec
- these values decrease with age } ~1-2 cc/sec per 5yrs

→ women

- “normal” } Qmax ~30 cc/sec
- not age dependent

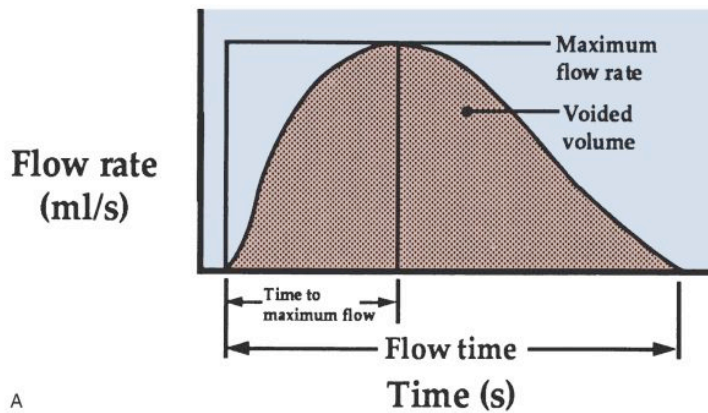
What non-anatomic factors affect Qmax?

- 1) age } decreases with age in men but no influenced by age in women (same in pregnancy)
- 2) sex } higher in women
- 3) time of day } higher at end of day
- 4) psychological inhibition
- 5) **voided volume } greatest effect on Q max**

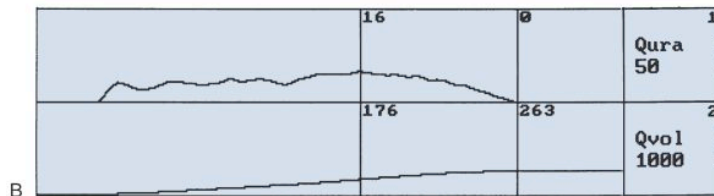
What is a N PVR?

→ no gold standard

- most normal, young patients have PVR <10 cc
- some guidelines say <100 cc is normal in older patients
- treatment of UTIs difficult with PVR >60 cc
- if asymptomatic with no complications (stones, UTI, etc), even PVR of 300 cc can be acceptable



A



B

→ UROFLOWMETRY CURVE

Cystometrogram (CMG)

What is the role of CMG?

- describes the filling phase of bladder function } limited by artificially high fill rate

What important data is obtained from CMG?

- 1) **capacity (300-500cc)**
- 2) **compliance (N is >12.5 mL/cm H₂O)**
- 3) **contractions, involuntary (stability)**
- 5) **sensation**
- 6) **contractility**
- 4) **continence/leakage (DLPP, VLPP)**
- 7) **complete emptying (PVR)**
- 8) **clinical obstruction**

What are the important points in setting up CMG?

- all systems must be zeroed to Patm
- if external transducers are used, reference point is upper edge of pubic symphysis
- make sure no bubbles in transducers or tubing } can affect pressure measurements
- physiologic liquid medium preferred } if too cold, can provoke overactivity
- **filling preferred at medium fill rate (10-100 cc/min)**
 - **physiologic/slow fill = <10 cc/min**
 - **rapid fill = >100 cc/min } provocative filling can be used to unmask OAB**

Why is liquid medium preferred over gas for CMG?

- 1) more physiologic
- 2) better able to control infusion rate
- 3) can't detect leakage of gas } LPP
- 4) hard to document volumes
- 5) gas is more compressible, which can affect pressure readings
- 6) can't perform voiding studies with gas
- 7) can't perform video UDS

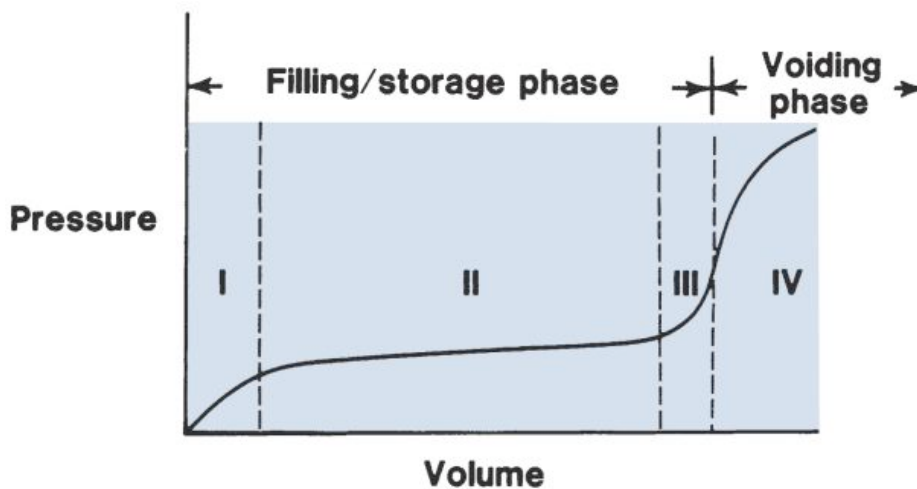
What are the 4 phases of a “normal” CMG tracing?

→ filling/storage

- 1) early rise to resting bladder pressure with initial filling
- 2) tonus limb } stable pressure during bladder filling w/o involuntary contractions
 } reflects viscoelastic properties of bladder wall (compliance)
- 3) rapid rise in pressure } filling exceeds limit of compliance of bladder wall
→ may want to add provocative measures (cough, Valsalva, jumping, fast fill, hand washing, running water)

→ voiding

- 4) initiation of voluntary voiding phase } voluntary bladder contraction



→ PHASES OF NORMAL CYSTOMETROGRAM

What are the potential technical issues in measuring pressures during CMG?

- measurement artifacts } air bubbles in transducer, kinked tubing, incorrect placement, migration of pressure catheters, catheter may prevent leakage
- infusion rate artifacts } rapid fill rate can result in lower compliance & uninhibited ctx's
- patient-related issues } uncooperative patient, outlet incompetence (constant leak), VUR
- irritating substances } catheter, fluid medium (temp, pH), hypersensitivity states

What are the “normal values” of CMG?

- overactivity } should have none, even with provocative maneuvers
- compliance } N is >12.5 mL/cm of H₂O
 } affected by fill rate, Pves, wall tension, and bladder volume
- capacity } 300-500 cc
- end-filling pressure } <10 cm H₂O above baseline
- DLPP } no real normal as you should have competent urethral sphincter + compliant bladder
- VLPP } no real normal as there should be no leakage with valsalva!!! (??? >90 cm H₂O)

What are the variables that can affect CMG results?

- 1) calibration
- 2) fill medium
- 3) fill rate
- 4) catheter size
- 5) presence of massive PVR
- 6) presence of outlet incompetence

What are the usual defined points of **SENSATION** recorded during CMG?

- | | | |
|--|---|---------------------------------|
| 1) first sensation of bladder filling (usually ~150cc) | \ | |
| 2) first desire to void (usually ~200) | } | N sensation, reduced sensation, |
| 3) strong desire to void | / | absent sensation |

What is **detrusor overactivity**?

- involuntary contractions of detrusor muscle during filling phase
- **spontaneous &/or provoked** } report # of ctx's, volume at which they occur, pressure amplitude, suppressible or not
- phasic detrusor overactivity } characteristic waveform that may or may not lead to incontinence
- terminal detrusor overactivity } single involuntary contraction at cystometric capacity that can't be compressed, leading to incontinence with bladder emptying
- **absence of documented overactivity on CMG does not rule its existence out**
 - up to 40% with urge incontinence do not have detrusor overactivity on CMG

What are the 2 main categories of **detrusor overactivity incontinence**?

- 1) neurogenic detrusor overactivity } used to be called "detrusor hyperreflexia"
- 2) idiopathic detrusor overactivity } used to be called "detrusor instability"
 - includes true idiopathic and non-neurogenic

What are the causes of detrusor overactivity?

- 1) Idiopathic detrusor overactivity
- 2) Neurogenic detrusor overactivity
 - supraspinal lesions
 - stroke
 - Parkinson's disease
 - hydrocephalus
 - brain tumours
 - traumatic brain injury
 - MS
 - suprasacral spinal lesions
 - SCI
 - SC tumour
 - MS
 - myelodysplasia/spina bifida
 - transverse myelitis
 - DM
- 3) Non-neurogenic detrusor overactivity
 - UTI
 - BOO
 - men } BPH, BN strictures
 - women } pelvic organ prolapse, post-incontinence sx, urethral diverticulum, primary BN, strictures
 - bladder tumour
 - bladder stones
 - FB
 - aging

What are the different measures of bladder **CAPACITY**?

- 1) functional } determined by voiding diary
- 2) maximum cystometric capacity } volume at which patient has strong desire to void and can't delay micturition any longer
- 3) maximum anesthetic capacity } volume bladder can be filled to under GA or epidural

How can one measure Pabdo in patients without a rectum?

- vagina
- colostomy/ileostomy

What are the urodynamic RFs associated with upper tract deterioration?

- DSD
- poor compliance
- BOO
- presence of VUR
- DLPP >40cm H₂O

What are the goals of managing high outlet resistance?

1) reduction of outlet resistance

- CIC
- urethral dilatation
- sphincterotomy
- vesicostomy

2) relaxation of bladder

- anticholinergics
- bladder augmentation

What are the other important measures recorded during provocative testing?

- 1) provoked involuntary contractions } eg stress induced detrusor overactivity
- 2) detrusor leak point pressure } **lowest Pdet at which urine leakage occurs, in the absence of any contractions or increased abdominal pressure**
(DLPP)
(passive leakage)
 - use smallest catheter possible (~6Fr)
 - **DLPP is a measure of the urethral resistance**
 - if outlet resistance high, a higher Pdet is needed to cause leakage/voiding
 - **DLPP >40 cm H₂O = high risk of upper tract damage**
 - not just degree of pressure, but time over which an elevated pressure is exerted is important
 - important not just to know DLPP but at what volume
 - high DLPP at high volumes may mean CIC
 - high DLPP at low volume may need augment
- 3) Valsalva LPP } **lowest Pves at which leakage occurs due to increased abdominal pressure, in the absence of any contractions** (active leakage)
(VLPP)
 - } aka abdominal LPP (ALPP)
 - } VLPP is higher with cough than with Valsalva
 - gives info on state of urethra
 - **abdo pressure only causes leakage w/ abN urethra**
 - abdominal pressure does not open a N urethral sphincter
 - **there is no normal VLPP!!!**
 - likely NOT urethral cause of incontinence if VLPP >150cm H₂O
 - on the other hand, low VLPP does not r/o detrusor component
 - **VLPP <60 cm H₂O = presence of significant ISD**
 - **VLPP 60-90 cm H₂O = equivocal (suggests ISD + urethral hypermobility)**
 - **VLPP >90 cm H₂O = urethral hypermobility + minimal ISD**
 - need to note the baseline Pves and subtract from Pves at leakage

What are the key steps in assessing VLPP during UDS?

- record lowest Pves when leakage occurs } preferably done in standing position
- ensure no contractions during filling CMG and with Valsalva
- use small catheter (3-5Fr), as large caliber may mask leakage
- fill to minimum 150-200cc
- gradually increase Pabdo w/ gradual constant Valsalva maneuver } if no leakage, get them to cough
- if still no leakage, fill and repeat at 300cc
- r/o cystocele and anxious patient

What are the potential causes of falsely elevated VLPP/ALPP?

- 1) cystocele
- 2) tense/anxious patient (contracts pelvic floor)
- 3) large catheter (resistance)
- 4) low volume in bladder
- 5) inability to strain

How can a cystocele affect VLPP?

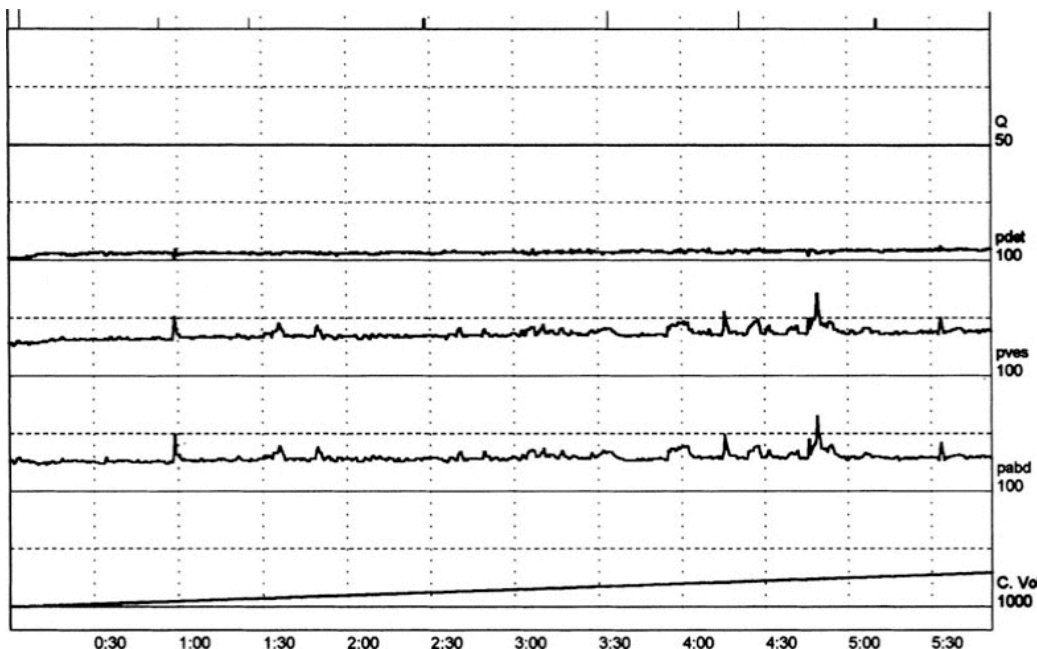
- **cystocele may artificially elevate VLPP**
- prolapsed bladder absorbs some of abdo pressure
- may also kink urethra causing obstruction
- **repair of a cystocele w/o addressing urethra may result in unmasking of incontinence**

What is the bethanechol supersensitivity test?

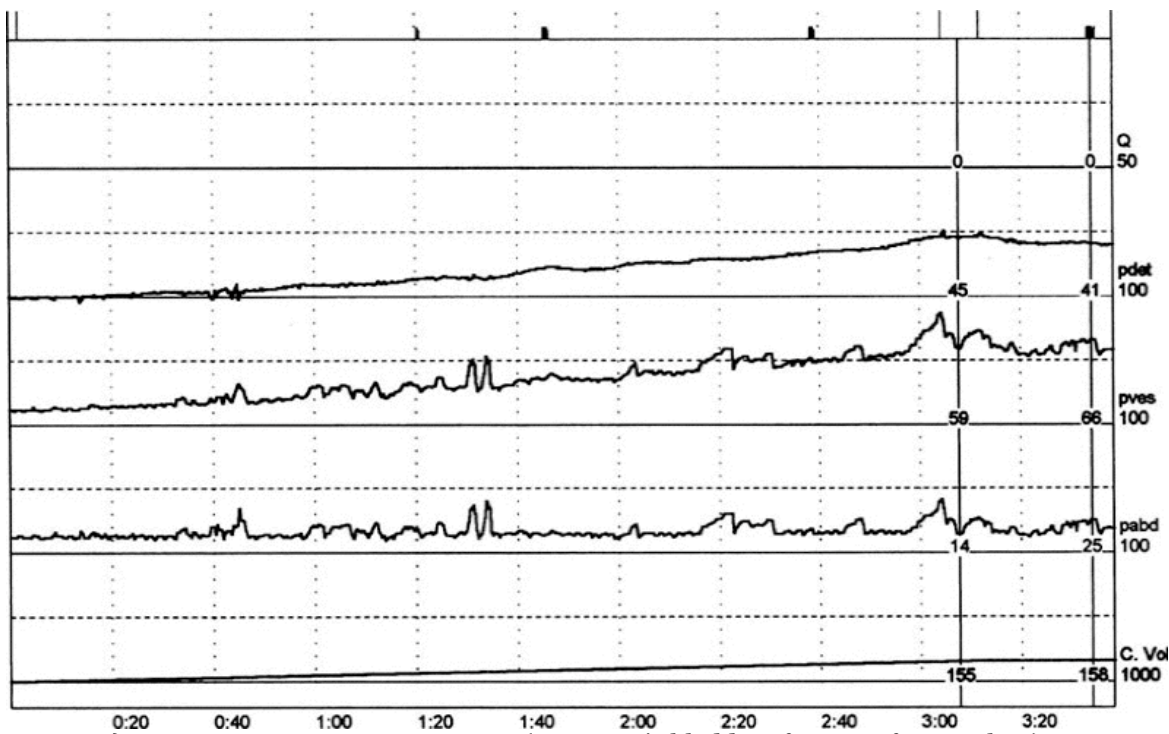
- described by Lapides then modified by Glahn **to determine if peripheral denervation**
- standard fluid infusion CMG at a filling rate of 1 cc/sec to a volume of 100cc
- repeated several times to get avg values of bladder pressure
- sc bethanechol administered (0.035 mg/kg)
- CMG repeated at 10, 20, 30 mins post injection
- neurologically intact bladder = pressure increase of <15 cm H₂O above control
- **“neurogenic bladder” = pressure increase of >15 cm H₂O**

What is the ice water test?

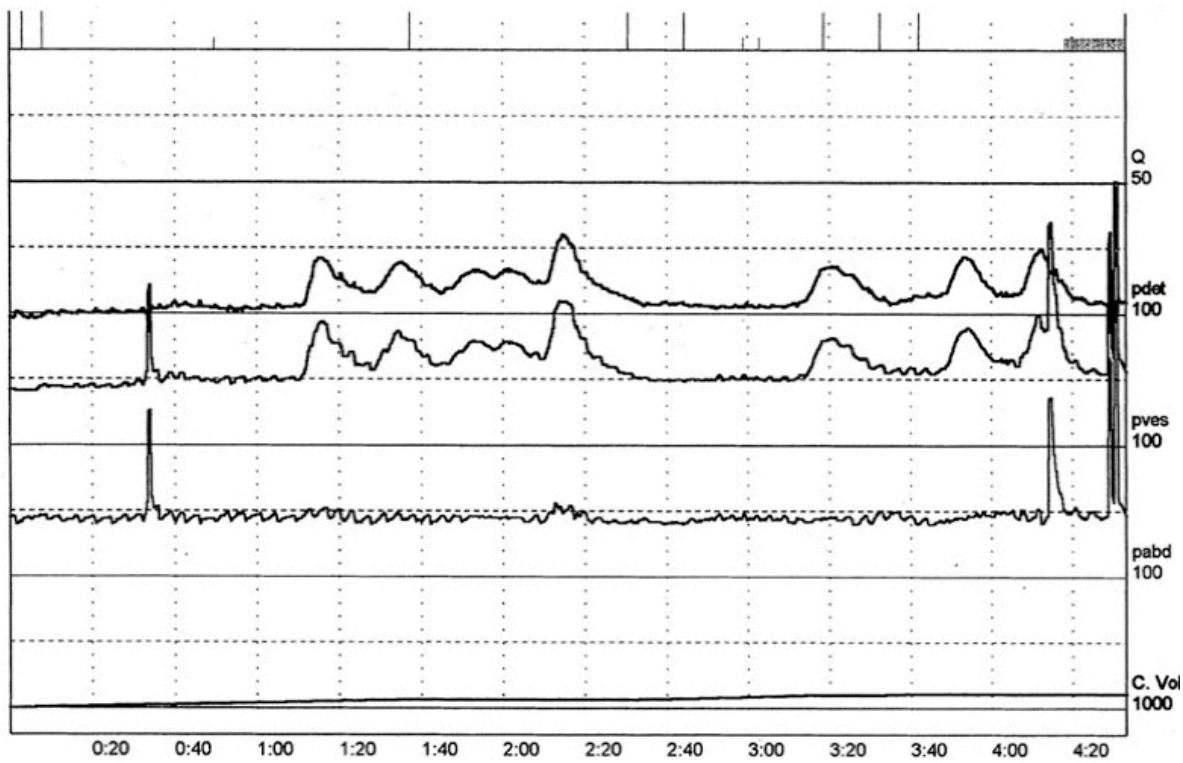
- described by Bors & Blinn **to differentiate UMN from LMN lesions**
- instillation of ice water into bladder
- involuntary bladder contraction is a +ve test
- **+ve test = UMN lesion } no inhibition of spinal reflex (elicited by cold temp) by supraspinal centres**
- -ve test = LMN or normal } can also be seen in young infant that can't suppress spinal reflex



- CMG } **NORMAL STUDY**
- } Pdet = 10cm H₂O at completion of fill with no detrusor overactivity



→ CMG } LOW BLADDER COMPLIANCE (neurogenic bladder after APR for rectal Ca)
 } Pdet = 45 cmH₂O at capacity of 155cc



→ CMG } DETRUSOR OVERACTIVITY (idiopathic)
 } multiple contractions during filling

Pressure-Flow studies (PFSs)

What is the role of PFSs?

- **to differentiate between low flow due to obstruction VS poor bladder contractility**
 - 25-30% with low flow rates have hypocontractility
- may also help identify those with high-pressure obstruction and normal flow rates
 - 7% of symptomatic men with $Q_{max} > 15 \text{ cc/sec}$ have obstruction
- obstruction can be structural (BPH or strictures) or functional (DSD)
- PFSs alone don't identify location of obstruction } need to add VUDS or sphincter EMG

Which men would benefit most from PFSs?

- if Sx is being considered } outcomes of outlet reduction surgery much better if BOO confirmed on PFS
 - **debatable } most say PFS can't predict outcomes**
- hx of neurologic disorder (eg CVA, MS, Parkinson's) } differentiate detrusor dysfunction from sphincter dysfunction
- younger men } determine functional disorder (eg BN dysfunction) from true obstruction

What are the common measurements taken during pressure-flow studies?

- premicturition pressure } pressure just before initial isovolumetric contraction
- **detrusor opening pressure** } pressure at onset of urine flow
- opening time } elapsed time from original rise in P_{det} to onset of flow
- maximal detrusor pressure (regardless of flow)
- **detrusor pressure at max flow** } pressure at measured Q_{max}
- **postmicturition/closing pressure** } pressure at end of measured flow
- **minimum voiding pressure**
- flow delay } time delay between change in bladder pressure and corresponding change in measured flow rate

What are the "normal values" of PFSs?

→ **no consensus**

→ men

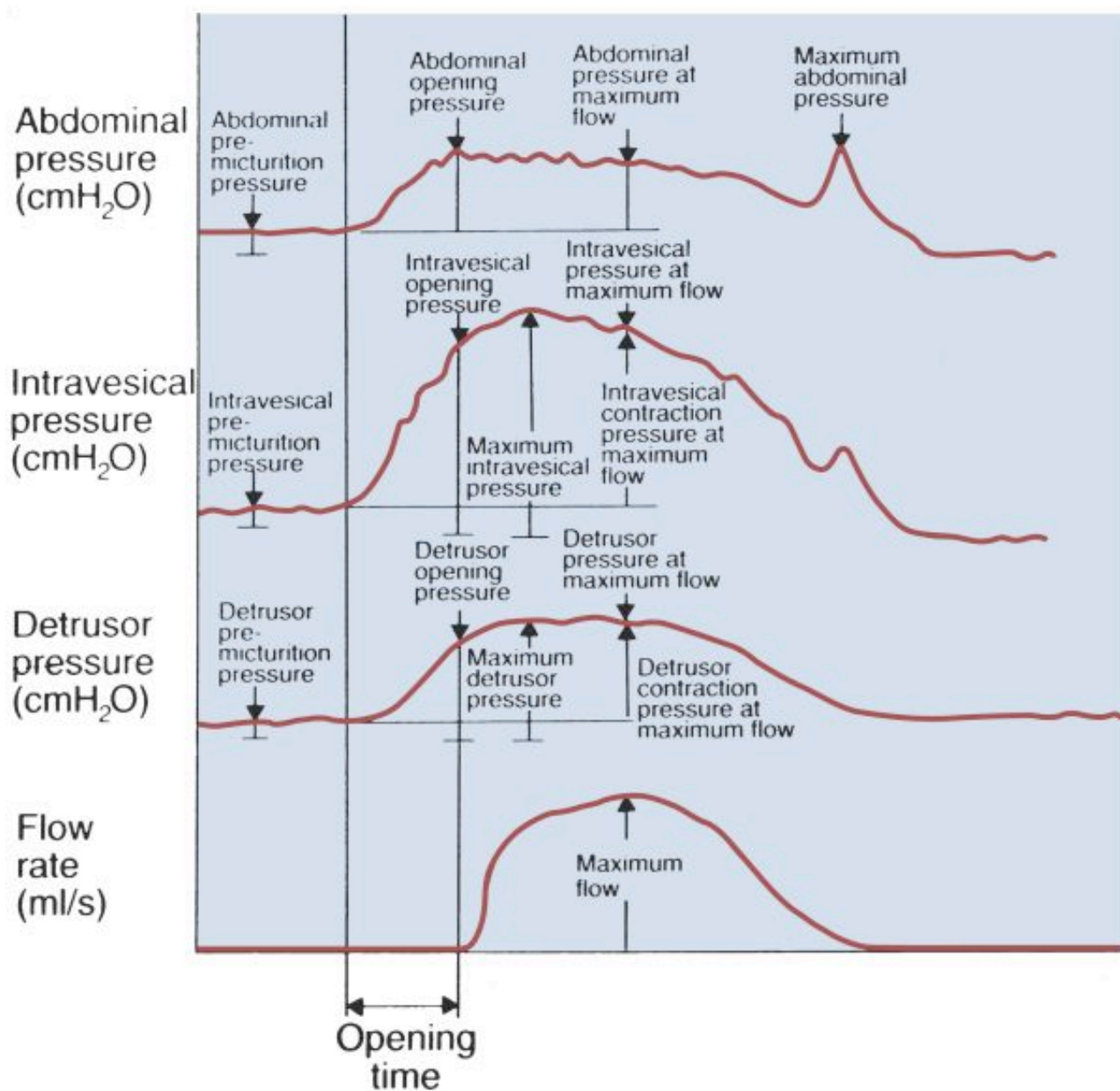
- easier to study } compare to those with BPH
- **$P_{det} < 40-60 \text{ cm H}_2\text{O}$** } if higher suggestive of obstruction
 - } however, obstruction can be present at lower values also
 - } low pressure, low flow is suggestive of poor compliance
- $Q_{max} > 15 \text{ cc/sec}$ } no gold standard reference values

→ women

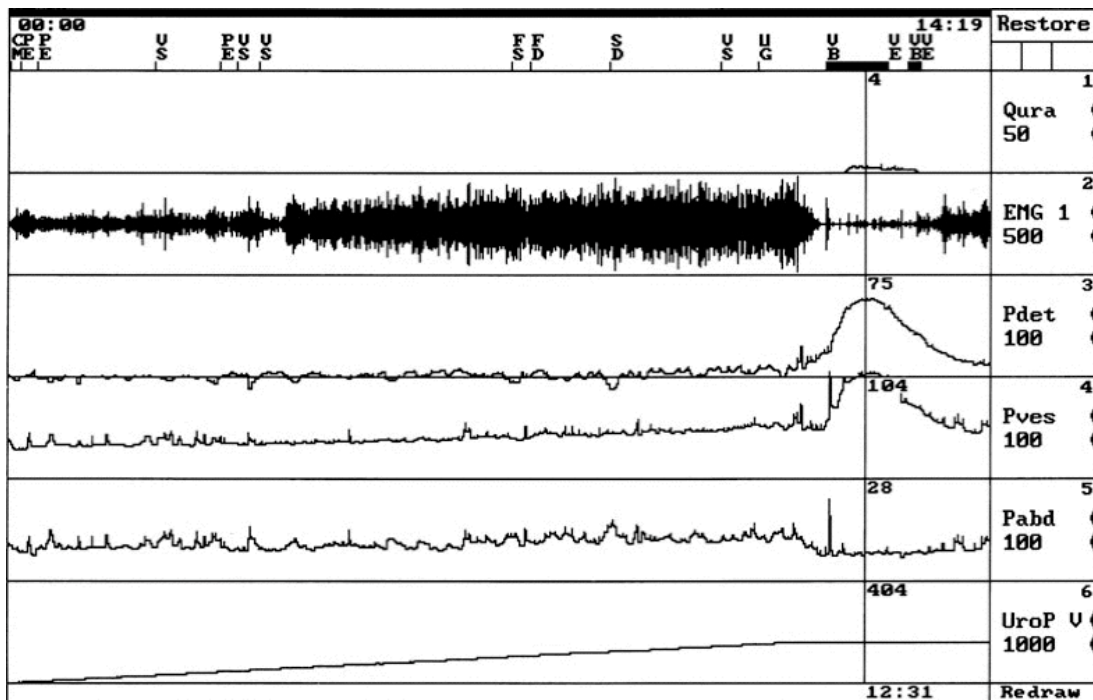
- harder to study } no reference model like BPH
- normal P_{det} with voiding is generally lower than men (**$< 20-30 \text{ cm H}_2\text{O}$**)
- normal Q_{max} is generally higher than men

What are potential causes of female obstruction?

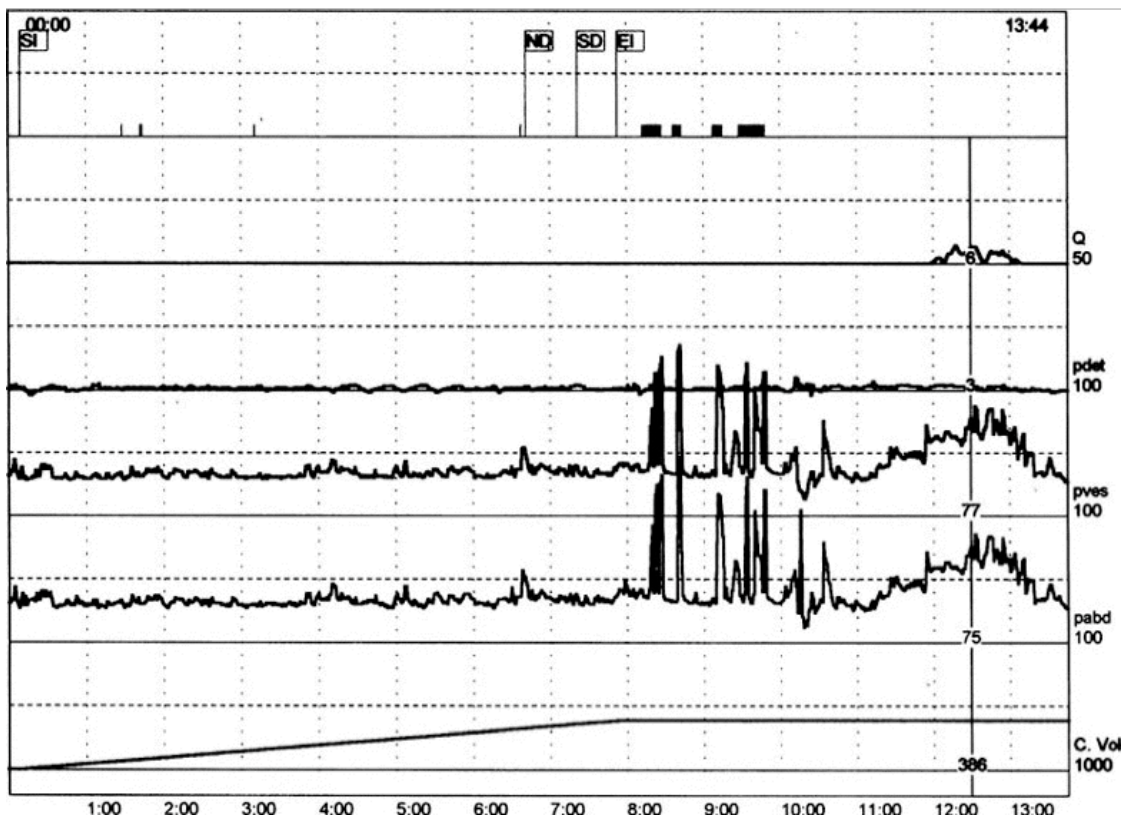
- dysfunctional voiding
- cystocele
- urethral stricture
- uterine prolapse
- urethral diverticulum
- rectocele
- iatrogenic post-incontinence surgery



→ PRESSURE FLOW STUDY (schematic)



→ PFS } OBSTRUCTION
 } Pdet = 75 cm H₂O with low flow Qura = 4cc/sec



→ PFS } POOR DETRUSOR CONTRACTILITY
 } Pdet = negligible and Qmax = 6cc/sec with Valsalva voiding (Pves & Pabd ~75 cm H₂O)

Nomograms

What are the common UDS nomograms used to diagnose the etiology of voiding dysfunction?

→ plotting pressures against flow **to discern obstruction from detrusor dysfunction**

1) Abrams-Griffiths (AG) nomogram

- developed in symptomatic men
- plots **Qmax vs PdetQmax**
- 3 regions } obstructed vs equivocal vs unobstructed
- patients in equivocal range can be refined based on minimum voiding pressure
 - based on slope ("AG number") } **AG number = $P_{det}Q_{max} - 2(Q_{max})$**
 - if >40 cm H₂O, then obstruction**
 - if <20 mm H₂O, then no obstruction**

2) Shafer nomogram

- plots **Qmax vs Pdet**
- PURR at minimal urethral opening pressure (Pmuo)
- allows grading of degree of obstruction (7)
 - 0 = no obstruction while 6 = severe obstruction
- can also plot grades of detrusor contractility (6)
 - Very Weak to Strong

3) Group-specific Urethral Resistance Factor nomogram

- developed from large group of adults with and w/o BOO
- URA number used to determine presence of obstruction

4) ICS Provisional nomogram

- similar to AG nomogram except smaller equivocal range (larger unobstructed range)
 - plots **Qmax vs PdetQmax**
- continuous grading of obstruction is possible by calculating the BOO index
 - **BOOI = AG number = $P_{det}Q_{max} - 2(Q_{max})$**
 - BOOI >40 = obstruction**
 - BOOI <20 = no obstruction**
- can also be categorized into 3 bladder contractility groups
 - use bladder contractility index (BCI) } **BCI = $P_{det}Q_{max} + 5(Q_{max})$**
 - BCI >150 = strong contractility**
 - BCI <100 = weak contractility**

What are the common measurements taken during Urethral Pressure Profile studies (UPPs)?

→ there are no urethral pressure measurements that can discriminate urethral incompetence from other disorders, that can measure severity of condition, or predict surgical success (!?! Useless)

- urethral pressure } fluid pressure needed to just open a closed urethra
- urethral pressure profile } graph showing intraluminal pressure along with length of urethra
- maximum urethral pressure
- urethral closure pressure profile } Purethra - Pves
- maximum urethral closure pressure (MUCP) } max difference between Purethra and Pves
 - } **ISD if MUCP is <20cm H₂O**
 - no correlation between low MUCP & SUI**
- fxn'l profile length } length of urethra along which urethral pressure exceeds Pves in women

What are the different UPP studies used?

- 6-10Fr fluid-filled catheter with circumferentially placed side holes is withdrawn from urethra at a rate of 0.5 cm/sec
- **urethral pressure = pressure needed to just keep open a closed urethra**
- ideally bladder pressure is also measured to nullify effects of any associated bladder ctx's
- 1) static UPP } study performed at rest
- 2) stress UPP } study performed with intermittent stress events superimposed
 - } increase in intra-abdo pressure should be transmitted to proximal urethra
 - } if this isn't seen on stress UPP, urethra may have fallen outside intra-abdo location (urethral hypermobility)
- 3) pressure transmission ratio (PTR) } increment in urethral pressure with stress as a % of the simultaneously recorded increment in Pves
 - } should exceed 100
 - } lower PTRs if incontinence + hypermobility
- 4) micturitional UPP } used to identify the presence and location of BOO
 - } similar to static UPP but patient voids as catheter is withdrawn
 - } compare bladder & urethral pressures to locate site of obstruction
 - **normal drop in pressure is 20-30 cm H₂O across the BN jxn with detrusor ctx's of 50-55 cm H₂O**
 - **more significant drop with catheter withdrawal across any site corresponds to site of obstruction**
 - } **in women, bladder and urethra are isobaric up to distal 1cm**

Video UDS

What is the role of Video UDS?

- most sophisticated form of evaluating patients with complex urinary tract dysfunction
- simultaneous evaluation of structure & function } can identify specific site of obstruction
- reduced chance of misinterpretation due to artifacts
- most important aspect of video UDS is the capability to measure urethral and bladder pressures while displaying them simultaneously with the corresponding fluoro images

What are the indications for Video UDS?

- complex LUTS with unclear UDS
- evaluation of concurrent anatomic abnormalities (eg cystocele, urethral diverticulum, etc)
- evaluation of concurrent pelvic organ prolapse
- **I ♥ PORNO**
 - **Incontinence** } degree of BN hypermobility, etc
 - **Post-op** } RP, APR, TAH
 - **Obstruction** } to help determine location
 - **Reflux**
 - **Neurogenic bladder dysfunction** } can find DSD, VUR, etc
 - **Other anatomic abnormalities** } tics, fistulae, stones

What important additional data is obtained from video UDS?

→ in addition to conventional UDS } ie uroflowmetry, CMG, pressure-flow studies

Upper tracts	VUR
Bladder	Capacity Shape Diverticula, trabeculations Cystocele Stones
Bladder neck	Position Open vs closed at rest Opening w/ urge/overactivity Descent w/ straining Contractures
Urethra	Presence of hypermobility BPH Strictures Diverticula
SUI	Sphincter activity (?DSD) Type (functional abN'ity) Severity (VLPP)
Other	Rectocele Vault prolapse Stones

→ also get more accurate VLPP measurement } can see exact moment of leakage

EMG studies

What is the role of EMG studies in UDS?

- sphincteric EMG can help evaluate striated sphincter complex and activity of the pelvic floor during bladder filling, storage, and voiding

→ **most important info is determining whether there is any DSD**

Where is the needle electrode placed for EMG studies?

→ **preferable to obtain readings from periurethral area**

1) periurethral area

→ men } 5 to 7.5cm needle placed through perineum toward apex of prostate, using finger in rectum as a guide

→ women } placed lateral to urethral meatus, advancing parallel to urethra for about 1-2cm
} transvaginal placement less painful

2) perineal floor

→ needle and wire electrodes may be placed in the bulbocavernosus muscle in men and the superficial anal sphincter in women

What are the indications for an EMG study?

→ **any patient with suspicion of discoordination between the sphincter & bladder**

- SCI
- Parkinson's
- MS
- spinal dysraphism
- multiple system atrophy
- post-pelvic or post-spinal surgery
- kids with voiding dysfunction + upper tract changes
- young F with urinary retention (r/o PCO syndrome)

What are the 4 parts of an EMG (kinesiologic) study?

- 1) volitional control } actively contract & relax sphincter
→ shows intact pyramidal tracts
- 2) bulbocavernosus reflex (BCR) is tested } squeeze glans/clitoris or pull on catheter and it should result in burst of EMG activity
→ shows intact sacral arc (pudendal S2-4)
- 3) bladder filling } should see increasing activity in sphincter
- 4) voiding } sphincter activity ceases just prior to onset of voiding
} no sphincter activity for duration of micturition
} once bladder is empty, sphincter EMG activity resumes
→ failure of sphincter to relax or stay relaxed during micturition is abN
 - if neurologic disease = DSD
 - if no neurologic disease = dysfxn'l voiding (pelvic floor hyperactivity)

What is the role of neurophysiologic EMG studies?

- designed to diagnose and characterize the presence of neuropathy or myopathy
- measure motor unit action potentials (MUAPs)
- **indication } bladder dysfxn of unknown cause in whom neuropathy is suspected**
→ **EMG studies good enough for most patients**
- normal } distal urethral sphincter MUAP has a biphasic or triphasic waveform
 - } amplitude of 50-300 mV
 - } frequency of 1-4 Hz
 - } duration of 3-5 mseconds
 - } <15% of activity is in form of polyphasic potential
- abnormal } complex waveform with larger amplitude and duration
 - } neuropathy implied when polyphasic activity is significantly >15%

What type of abnormal EMG waveforms are seen in patients with neurologic conditions?

- fibrillation potentials
- complex polyphasic potentials (>5 deflections)
- complex repetitive discharges
- positive sharp waves
- bizarre high frequency forms
- DSD

What is DSD?

- detrusor-sphincter dyssynergia
- **failure of sphincter to relax or stay relaxed during voiding in pts w/ neurologic disease**
 - if no neurologic disease, condition is called **pelvic floor hyperactivity or dysfunctional voiding (Hinman syndrome)**
 - aka "non-neurogenic neurogenic bladder" or "pseudodyssynergia"
- typically in pt w/ **suprasacral injury ("SMC-T")** } interruption of spinobulbar-spinal pathways
→ **suprasacral SCI, MMC, CP, transverse myelitis, etc**
- ranges from crescendo contraction to failure of relaxation

What EMG findings are found in Parkinson's disease?

- tremor, rigidity, akinesia, postural instability
- **sphincter bradykinesia ("pseudodyssnergia")**
 - delay of sphincter relaxation at onset of voiding due to skeletal muscle hypertonicity

What can be seen on EMG in patient with detrusor overactivity?

- normal response to involuntary contraction is contraction of EUS to prevent leakage
 - similar appearance to DSD } different because voluntary contraction of EUS

AMBULATORY URODYNAMICS

What are the advantages & disadvantages of ambulatory urodynamics monitoring (AUM)?

→ advantages

- **greatest benefit when conventional UDS can't reproduce symptoms**
- utilizes physiologic filling and voiding
- reproduces patient's everyday activities
- more sensitive for detection of unstable detrusor contractions
- urine is at N body temp
- avoids unphysiologic circumstances of conventional UDS

→ disadvantages

- need to keep catheters in place for long period of time
- lack of minute to minute control on validity of signals
- heavy reliance on patient compliance and education
- time consuming and labour intensive
- reference values on conventional UDS may not apply to AUM
 - **filling pressures tend to be significantly lower than on conventional UDS**
 - **low compliance seen on conventional UDS may be due to unphysiologic filling with cold fluid**

****Causes of Overactive/Unstable/Involuntary Bladder Contractions****

Neurogenic overactivity (Detrusor Hyperreflexia)	Non-Neurogenic/Idiopathic overactivity (Detrusor Instability)
Suprasacral Spinal Lesions (PMC-Sacral) SCI MS Spina bifida Transverse myelitis MMC Supraspinal Lesions CVA Brain tumor Parkinson's disease Shy-Drager Hydrocephalus MS CP General DM	Idiopathic urethral obstruction UTI/inflammation (prob. most common) BOO: BPH (men), urethral stricture/scar (women) Bladder stones Bladder tumor Foreign body Sphincteric incontinence Ageing

****DDx for Changes in Bladder Compliance****

Low Compliance Pathologic Causes	High Compliance
Decreased Accommodation - ↑ Collagen 1. infectious: TB, schistosomiasis 2. radiation 3. chronic BOO 4. defunctionalization - prolonged catheterization: muscular hypertonia, mucosal and mural changes - defunctionalization 5. idiopathic: interstitial cystitis 6. surgery	1. prolonged and gradually progressive delayed voiding 2. sensory impairment; most commonly DM or pernicious anemia (B12), EtOH w/ peripheral neuropathy 3. SCI – period of spinal shock lasting 6-8 weeks post injury
Increased Tone – Neurogenic 1. MM 2. Shy-Drager 3. Thoracolumbar SCI 4. surgery: hysterectomy, APR	Artificially (False +ve) Causes of decreased 1. filling beyond distensibility limits (stage III of CMG) 2. rapid filling rate (<i>exceeds rate of stress relaxation</i>)

(McGuire 1981, Ghoneim 1989, Steinkohl 1989, Zoubek 1989, McGuire 1994)

Chapter #59 – Lower GU Tract Dysfunction in Neurologic Injury and Disease

OBJECTIVES

List common patterns of voiding dysfunction seen with various neurologic diseases (CHART).

Disorder	Detrusor Activity	Compliance	Smooth Sphincter	Striated Sphincter	Sensation
CVA/brain tumour	overactive	N	synergic +/- VC	synergic	may be ↓'d
Cerebral palsy	overactive	N	synergic	synergic (25% DESD)	
Parkinson's	overactive (few are acontractile)	N	synergic	synergic (bradykinesia)	
Multi-system Atrophy	overactive	N (may be ↓'d)	open	synergic (may be denervated)	
MS	overactive (20-40% areflexia)	N	synergic	synergic (30-65% DESD)	
Suprasacral SCI	overactive	N	synergic (DSD if T6 or above)	DESD	no sensation
auto. dysreflexia	overactive	N	dyssynergic	DESD	
Sacral SCI	areflexic	N (may be ↓'d)	competent, nonrelaxing (may become open)	fixed	
Myelodysplasia	areflexia	N (may be ↓'d)	open	fixed (10% DESD)	
Tabes dorsalis, pernicious anemia	impaired	N	synergic	synergic	1° issue is loss of sensation
DDD	areflexic	N	competent, nonrelaxing	synergic	
Post-radical Pelvic sx	impaired or areflexic	↓'d or N	open	fixed	
DM	any of O, A, I	N or ↑'d	synergic	synergic	

Diseases assoc'd w/ areflexia.

→ "SIDS MD"

- Sacral SCI
- Iatrogenic (post-op)
- DM
- Spina Bifida
- MS (20-40%)
- DDD

Diseases assoc'd w/ poor compliance.

→ "SIMS"

- Sacral SCI
- Iatrogenic
- MSA
- Spina Bifida

Diseases assoc'd w/ DESD.

→ "SMCS - T"

- Suprasacral SCI
- MS (30-65%)
- Cerebral palsy (25%)
- Spina bifida (10%)
- Transverse myelitis

What are the 5 main voiding parameters to be assessed in neurologic disease or injury?

- 1) detrusor activity } N, overactive, areflexic, impaired contractility
- 2) detrusor compliance } N, decreased, increased
- 3) smooth sphincter activity } synergic, dyssynergic
- 4) striated sphincter activity } synergic, dyssynergic, bradykinetic, impaired voluntary control, fixed tone
- 5) sensation } N, absent, impaired

GENERAL PATTERNS OF NEUROPATHIC LOWER URINARY TRACT DYSFUNCTION

What are the 3 main factors that determine the affects of a specific neurologic lesion/injury?

- 1) area(s) of the nervous system affected
- 2) physiologic function(s) and the contents and location of area(s) affected
- 3) whether lesion or process is destructive or irritative

What are the general features of lesions ABOVE THE BRAIN STEM?

- **detrusor overactivity** } may develop detrusor areflexia
- **synergic sphincter** function (smooth and striated) } MS & CP can get DESD
- **sensation usually N** } may be deficient

What are the general features of lesions from SPINAL CORD LEVEL T6 TO S2 (SUPRASACRAL)?

- after recovery from spinal shock
- **detrusor overactivity**
- **smooth sphincter synergy** } if lesion is above T6, then may also get dyssynergy
- **DESD**
- **no sensation**

What are the general features of lesions BELOW SPINAL CORD LEVEL S2 (SACRAL)?

- after recovery from spinal shock
- **detrusor areflexia** } may develop decreased compliance
- **competent, non-relaxing smooth sphincter**
- **fixed EUS** (no voluntary control)

What are the general features of lesions interrupting PERIPHERAL REFLEX ARC?

- **detrusor areflexia** } may develop decreased compliance
 - **open, incompetent smooth sphincter**
 - **fixed EUS** (no voluntary control)
 - **motor & sensory loss**
- \ } may be similar to distal SCI
/ or nerve root injury

What is the role of neuroplasticity in voiding dysfunction?

- 1) influences chronic changes in neural organization of micturition reflex that occurs after complete SCI above S2
- 2) influences changes in peripheral neural organization that occur after damage to or transection of peripheral parasympathetic innervation
- 3) can influence structural changes
 - increased contractile protein synthesis
 - hypertrophic bladder tissue growth
 - increased type 3 collagen to type 2 collagen ratio

\ } may also be due to overdistension
/ and ischemia
- 4) **may account for persistence of clinical symptoms even after initial stimulus for dysfunction has been removed or corrected**

How do structural changes influence voiding dysfunction?

- 1) decreased compliance } changes in extracellular matrix (eg type 3 collagen)
- 2) appearance of phasic bladder overactivity } myogenic or neurogenic

What are the causes of detrusor overactivity?

- 1) Idiopathic detrusor overactivity
- 2) Neurogenic detrusor overactivity
 - supraspinal lesions
 - stroke/CVA
 - Parkinson's disease
 - hydrocephalus
 - brain tumours
 - traumatic brain injury
 - MS
 - suprasacral spinal lesions
 - SCI
 - SC tumour
 - MS
 - myelodysplasia
 - transverse myelitis
 - DM
- 3) Non-neurogenic detrusor overactivity
 - UTI
 - BOO
 - M } BPH, BN strictures
 - F } pelvic organ prolapse, post-incontinence sx, urethral tics, primary BN, strictures
 - bladder tumour
 - bladder stones
 - FB
 - aging

DISEASE AT OR ABOVE THE BRAIN STEM

What are the urinary features of “cerebral shock”?

- early period post-CVA
- **urinary retention from detrusor areflexia**

What are the lower urinary tract features after **CVA/STROKE**?

- long-term features
- 1) clinical
 - **urgency, frequency** } nocturnal frequency is most common finding (35%)
 - **incontinence** } unable to inhibit contractions by voluntary contraction of EUS
 - } unable to sense bladder filling and impending bladder contraction
 - occurs in 10-20% long-term
 - incontinence at time of presentation with CVA is bad prognostic feature
 - associated with worse overall outcomes (infections, death, etc)
 - persistent retention (rare)
- 2) UDS
 - **phasic detrusor overactivity**
 - detrusor areflexia or hypocontractility (rare)
 - **synergic sphincter activity**
 - may lose voluntary control of EUS if involves cerebral cortex or internal capsule
 - voluntary control preserved if only involves basal ganglia or thalamus
 - smooth sphincter activity is unaffected (synergic)
 - **N compliance**
 - **N sensation** (can be decreased)

What are the lower urinary tract features of **TBI**?

→ do not always have voiding dysfunction

→ if symptomatic, usually have initial period of detrusor areflexia (retention)

- lesion above PMC } **involuntary contractions** most common
 } **synergic sphincter activity**
- isolated brain stem lesion } involuntary contractions
 } DSD

What are the lower urinary tract features of a **BRAIN TUMOUR**?

→ related to localized area involved not type of tumour

→ superior frontal lobe is most commonly associated with voiding dysfunction

1) clinical

- **incontinence**
- retention (more common with posterior fossa tumours)

2) UDS

- **detrusor overactivity**
- **synergic sphincter activity**
- **N compliance**

What are the lower urinary features of **DEMENTIA**?

→ **incontinence** is the most common finding

→ cause unclear } ?detrusor overactivity

- } ?normal function but untimely micturition reflex

} ?normal function but unable to appreciate socially appropriate times to void

What are the lower urinary tract features of **CEREBELLAR ATAXIA**?

→ poor coordination, depressed DTRs, dysarthria, dysmetria, choreiform movements

1) clinical

- **incontinence** } rarely may develop retention or high PVRs

2) UDS

- **detrusor overactivity** } may develop detrusor areflexia
- **synergic sphincter activity** } DSD can occur but is uncommon
- **N compliance**

What are the lower urinary tract features of **CEREBRAL PALSY**?

→ delayed gross motor development, abN motor performance, altered muscle tone, abN posture, exaggerated reflexes } non-progressive disease

→ most with CP have normal voiding function

→ ~25% have voiding dysfunction } more common with spastic tetraplegia, low intellect

- 1) clinical

- **incontinence**

2) UDS

- **detrusor overactivity (80% of those with abN UDS)**
- **synergic sphincters** } occasionally see **DSD (25%)**
- **N compliance**

What are the lower urinary tract features of **PARKINSON'S DISEASE**?

- dopamine deficiency in nigrostriatal pathway (substantia nigra pars compact)
- tremor, rigidity, akinesia, postural instability
- **voiding dysfunction occurs in 35-70%**
- 1) clinical
 - **frequency, urgency (more common than incontinence)**
 - **incontinence**
 - 25% have "obstructive" symptoms (giving apomorphine can distinguish from BPH)
- 2) UDS
 - **detrusor overactivity** (loss of inhibition of micturition reflex by basal ganglia)
 - may have **impaired contractility** but uncommon (**TURP may NOT help**)
 - **synergic smooth sphincter activity**
 - **synergic EUS } bradykinesia results in pseudodyssynergia**
 - **N compliance**
 - **N sensation**

What are causes of parkinsonism?

- parkinson's disease } **asymmetrical symptoms & signs, + resting tremor + good response to L-dopa differentiates PD from other causes**
- multi-system atrophy (MSA) } includes Shy-Drager, striatonigral degeneration, etc
- progressive supranuclear palsy
- cortical-basal ganglionic degeneration
- vascular parkinsonism
- Lewy body dementia

What are the lower urinary tract features of **MULTI-SYSTEM ATROPHY (MSA)**?

- progressive neurodegenerative disease of unknown etiology } poor prognosis
- can have parkinsonism-type or cerebellar-type MSA
- middle age onset with M = F
- 1) clinical
 - **incontinence (>75%)** \ **with progression of disease, may develop difficulty**
 - frequency, urgency / **initiating & maintaining voiding (poor prognosis)**
 - ED
- 2) UDS
 - **detrusor overactivity**
 - **open smooth sphincter (ISD)**
 - **synergic EUS but becomes denervated**
 - **N compliance** } may develop decreased compliance as MSA progresses
 - **N sensation**

What is Shy-Drager syndrome?

- **orthostatic hypotension + anhidrosis + cerebellar & parkinsonian dysfxn** } **likely late-stage MSA**
- voiding dysfunction and ED common

What features help differentiate MSA from Parkinson's disease? } } } "SPICES worse after TURP"

- 1) urinary Symptoms present before or w/ parkinsonism
 - majority with PD have Dx before onset of urinary symptoms (~3yrs later)
- 2) PVR is significant in SD
- 3) Incontinence much more common (75%)
 - most with PD have urgency & frequency without incontinence
- 4) Compliance is low with SD
- 5) ED before or presents with parkinsonism
 - majority with PD have Dx before onset of ED
- 6) Sphincter is open & smooth (denervated – abN EMG)
 - PD patients have synergic sphincters } may get bradykinesia
- 7) **worsening voiding dysfunction after urologic Sx (eg TURP)**
 - most with PD do not get worse after Sx (issue is that TURP may not help if they have areflexia)

DISEASES PRIMARILY INVOLVING THE SPINAL CORD

What are some important features of SCI?

- complete anatomic transection of SC is rare
- degree of neurologic deficit varies with level & severity of injury
- spinal cord level DOES NOT EQUAL spinal column level
 - sacral spinal cord starts at T12-L1 vertebrae
 - cauda equina starts at L2 vertebrae
- **MVA is the most common cause (36%)**
 - violence is 2nd, falls 3rd & sports-related injury 4th
- **males represent ~75%**
- **incomplete quads constitute the largest group (30%)**
 - complete paraplegics are 2nd, complete quads are 3rd, incomplete paraplegics 4th
- leading causes of death in SCI patients are pneumonia, septicemia, CVD, accidents, suicide
 - respiratory (~20%) & cardiac (~20%) disease most common
- SCI patients living longer than in the past } increasing prevalence (incidence about same)

What are the acute systemic features of a SCI? (AUA Update #25 - 2008)

- brief initial period } tachycardia + HTN
- neurogenic shock (prolonged period) } bradycardia + hypoTN + ↓'d CO & PVR

What are the features of "spinal shock"?

- period of decreased excitability of SC segments at and below level of lesion
- usually lasts 6-12 weeks } shorter if incomplete lesion
- absent DTRs + flaccid muscle paralysis below level of lesion
- 1) clinical
 - **retention** } incontinence only if overflow
- 2) UDS
 - **detrusor areflexia**
 - synergic smooth sphincter
 - decreased synergic EUS tone } no voluntary control + loss of N guarding reflex
 - closed, competent BN
 - **hypercompliance**
 - **absent sensation**

What are the 4 potential mechanisms for recovery of detrusor contractions after suprasacral SCI?

- 1) elimination of bulbospinal inhibitory pathways
- 2) strengthening of existing synapses or formation of new one from axonal sprouting in the SC
- 3) changes in synthesis, release, or actions of NTs
- 4) alterations in afferent input from bladder

What structural changes occur after suprasacral SCI?

- 1) ↑'d sensitivity of C-fiber afferents
- 2) enlargement of dorsal root ganglion cells
- 3) ↑'d electrical excitability of afferents (change in type of Na channels)
- 4) ↑'d []'s of glutamate, glycine, and taurine
- 5) disruption of urothelium barrier function
- 6) change from low affinity M1 to high affinity M3 receptors at cholinergic nerve endings
- 7) ↑'d release of ATP from urothelium
- 8) ↑'d SC nerve growth factor
- 9) alterations in smooth muscle myosin heavy chain gene expression

List the important components of the neurologic exam in a patient with a SCI. (AUA Update #25 - 2008)

- 1) perineal sensation } tests pudendal afferents
- 2) baseline anal sphincter tone } increased tone = suprasacral lesion
 } reduced tone = sacral/peripheral lesion
- 3) lower extremity spasticity
- 4) voluntary anal sphincter contraction } tests pudendal efferents & suprasacral control
- 5) BCR } tests pudendal nerve & sacral micturition centre (S2-S4)
 } absent in 20-30% of N patients
- 6) anal sphincter reflex

What are the expected UDS findings of SCI? (AUA Update #25 - 2008)

→ **COMPLETE SUPRASACRAL SCI (above T6)**

detrusor overactivity + dyssynergic smooth sphincter + DESD

→ **COMPLETE SUPRASACRAL SCI (below T6)**

detrusor overactivity + N smooth sphincter + DESD

→ COMPLETE SACRAL SCI

detrusor areflexia (+/- poor compliance) + tight BN + fixed EUS

→ PERIPHERAL LESION

detrusor areflexia (+/- poor compliance) + open BN + fixed EUS

List ways to assess the upper tracts in patients with SCI. (AUA Update #25 - 2008)

- 1) renal scan (preferred)
 - 2) renal U/S
- creatinine is NOT sensitive enough to detect early deterioration

List the GU goals of management of a SCI patient. (AUA Update #25 - 2008)

- 1) preserve & protect upper tracts
- 2) minimize LUT complications
- 3) treat incontinence
- 4) mgt plan that is safe and also maintains QOL

What are the lower urinary tract features of SUPRASACRAL SC LESIONS?

→ correlation between somatic neurologic findings & UDS findings is not exact

→ DESD implies lesion that interrupts neural axis between PMC and sacral SC

- 1) clinical
 - **spastic muscles below** level of lesion + **hyper-reflexic DTRs** & abN plantar reflexes
 - **incontinence**
 - PVR
- 2) UDS
 - **detrusor overactivity** } may get detrusor areflexia
 - **synergic smooth sphincter** } **dyssynergic smooth sphincter if at or above T7**
 - **DESD** } absent or weak guarding reflex in complete lesions
 - N compliance
 - absent sensation below level of lesion

What are the goals of management of voiding dysfunction associated w/ SUPRASACRAL LESIONS?

→ Rx should be mainly based on UDS findings (~30% discordance b/w UDS and SCI level)

→ storage failure + emptying failure

- 1) make into primarily emptying failure } meds (eg anti-cholinergics, botox, etc) or Sx (augment, etc)
 - CIC
 - sphincterotomy + external collecting device
 - stenting + external collecting device
 - intrasphincteric botox + external collecting device
- 2) watch for autonomic dysreflexia for lesions above T6-T8
- 3) identify and correct potential urologic complications with careful evaluation and close f/u

What is autonomic dysreflexia?

- acute massive disordered sympathetic response to noxious stimulus in pts w/ **SCI above T6-T8**
 - **only after spinal shock phase & must have viable/intact distal cord**
 - syndrome of exaggerated sympathetic activity in response to **stimulus below level of lesion**
 - } unable to inhibit reflex sympathetic outflow from afferent stimulation
 - } uninhibited **sympathetic outflow below lesion** (vasoconstriction of splanchnic bed)
 - + reflex **parasympathetic outflow above level of lesion**
- H/A + HTN + sweating/flushing above lesion + cool skin below lesion + reflex bradycardia
 - can have tachycardia or arrhythmia also
- noxious stimulus } bladder or rectum most common
 - } bladder distension (most common), constipation, instrumentation, catheter change, stone, sex, pain from long bone fractures, pressure sores
- have detrusor overactivity + dyssynergic smooth sphincter + DESD

What is the management of autonomic dysreflexia?

- 1) prevention
 - identify those at risk & prevent potential noxious stimuli (eg AUR, constipation, pressure sores)
 - careful monitoring during provocative procedures
 - prophylactic meds } nifedipine 10-20mg crushed sublingual or swallow 30 mins prior
 - } terazosin (5mg po qHS), prazosin (3mg po bid)
 - spinal anesthesia
- 2) treatment
 - remove noxious stimuli (stop cystoscopy, foley for retention, etc) \ this alone usually will
 - raise head of head & remove tight clothing / reverse symptoms
 - monitor vitals
 - nifedipine 20mg crushed/chewed sublingual } hydralazine if CCB doesn't work
 - atropine 1mg iv for reflex bradycardia (HR <45)
 - topical 2% nitropaste 1-2 inches above level of lesion
 - iv nitroprusside if still refractory
 - can do spinal anesthetic also

What are some options for refractory autonomic dysreflexia?

- sympathectomy
- sacral neurectomy
- dorsal root ganglionectomy
- sacral rhizotomy

What are the lower urinary tract features of SACRAL SPINAL CORD LESIONS?

→ correlation between somatic neurologic findings & UDS findings is not exact (~30% discordance)

- 1) clinical
 - varying degrees of **flaccid paralysis** + **decreased DTRs** below level of lesion
 - **retention**
- 2) UDS
 - **detrusor areflexia** } may see detrusor hyperreflexia
 - **competent, non-relaxing smooth sphincter** } may become open
 - **fixed EUS** } no voluntary control
 - high or N compliance } **may develop ↓'d compliance over time**
 - absent sensation below level of lesion

What are the goals of management of voiding dysfunction associated with SACRAL LESIONS?

- **Rx should be mainly based on UDS findings (~30% discordance b/w UDS and SCI level)**
- mainly emptying failure
- 1) maintain low storage pressure while managing emptying failure
 - CIC whenever possible
 - meds to promote emptying not very successful (eg bethanechol)
 - neuromodulation can be used to promote emptying in certain cases (limited data)
 - surgical options (ileal chimney +/- BN closure, continent catheterizable stoma, etc)
- 2) identify and correct potential urologic complications with careful evaluation and close f/u

What are the RFs and potential complications of voiding dysfunction associated with SCIs?

→ RFs

- bladder overdistension
- loss of compliance (<12.5 cc/cm)
- high DLPP (<40 cm H₂O)
- DESD

→ complications

- VUR
- infections (UTI, pyelo)
- stones (upper and lower tract)
- renal failure

How common is VUR associated with SCI?

→ **secondary VUR found in 15-25% } more common with suprasacral SCIs**

- can lead to chronic upper tract deterioration } affects long term survival
→ upper tract deterioration can occur even without VUR

- contributing factors include:

- 1) high intravesical pressure during filling and emptying
- 2) infections

Rx → decrease storage & emptying pressures

- meds (eg anticholinergics)
- urethral dilatation (MMC patients)
- neuromodulation
- augmentation cystoplasty
- sphincterotomy
- deafferentiation

→ treat VUR directly if these fail

- reimplant
- Deflux injections
- TUU (unilateral VUR)

How common are UTIs in SCI patients?

→ 75% of patients in 1st year after initial hospitalization

- **only Rx bacteriuria if signs or symptoms present } use ABx w/ least impact on N flora**
- minimum 5days Rx } 1-2 wks if reinfection or relapse
- correct functional or structural RFs
- prophylactic ABx only if recurrent UTIs with no known cause + dilated upper tracts
- no role for prophylactic ABx for indwelling foley
- use of prophylactic ABx for CIC patients is controversial

What are some specific issues with SCIs in women?

- menopause may resemble autonomic dysreflexia
- incontinence and UTIs worse even in healthy aging women
- lack of appropriate external collecting device for women
- CIC easier for women
- use of indwelling catheter associated with highest complications

What is the risk of bladder Ca in SCI patients? (includes AUA Update #25 – 2008)

- ~25x higher incidence than general population } controversial
- occurs earlier than general population
- **SCC may represent higher proportion of bladder tumours cf TCC (debatable)**
- tends to present at more advanced stage
- RFs include:
 - chronic indwelling catheter (5x more than CIC)
 - bladder stones
 - chronic UTIs

What are the lower urinary tract features of ACUTE TRANSVERSE MYELITIS?

- rapidly developing condition with motor, sensory, and sphincter abnormalities
 - no signs of SC compression or other neurologic disease
 - **unknown etiology** } parainfectious, autoimmune, vascular, demyelinating
 - condition **stabilizes in 2-4 wks and is not progressive afterwards**
 - variable recovery with some residual neurologic deficits
- nature of voiding dysfunction similar to SCI } better prognosis and recovery
- acute UDS
 - detrusor areflexia } may also get detrusor overactivity
 - **DESD**
 - **poor compliance**
 - most are in retention

What are the lower urinary tract features of MULTIPLE SCLEROSIS (MS)?

- immune mediated neural demyelination with axonal sparing in brain and SC
 - scattered plaques throughout white matter (1-40mm)
 - most commonly involve lateral corticospinal (pyramidal) & reticulospinal columns of C-spine
- 50-90% complain of voiding dysfunction at some time } 2x more common in F
- 1) clinical
 - **incontinence, urgency, frequency**
 - may develop retention in a small subset (DESD)
- 2) UDS
 - **detrusor overactivity + synergic EUS (40%)** \ overactivity is most
 - **detrusor overactivity + DESD (30-65%)** / common UDS finding
 - can get impaired detrusor contractility or **detrusor areflexia in 20-40%**
 - synergic smooth sphincter activity
 - N compliance
 - N sensation
- DESD most predictive of upper tract deterioration in men with MS
- significant proportion of MS patients will develop changes in compliance and UDS features
- avoid irreversible therapeutic options

What are the RFs for urologic complications in MS patients?

- 1) DESD in men
- 2) high detrusor filling pressure (>40 cmH₂O)
- 3) indwelling catheter

What are the lower urinary tract features of NEUROSPINAL DYSRAPHISM?

- MMC accounts for >90% of spina bifida } 2% cervical, 5% thoracic, 26% lumbar, ~50% lumbosacral, 20% sacral
- voiding dysfunction in >90% of patients with MMC
- level of lesion correlates poorly with UDS findings
- 1) clinical
 - **retention**
 - SUI
- 2) UDS
 - **detrusor areflexia (usually lumbosacral)** } can see overactivity (if higher lesion)
 - open bladder neck
 - **fixed EUS } 10% have DESD**
 - N compliance } **40% have ↓'d compliance**

What are the goals of management of voiding dysfunction associated with SPINAL DYSRAPHISMS?

- **management should be mainly based on UDS findings because neurologic findings & UDS findings don't always match**
- 1) achieve continence } periurethral injections (esp for F), slings, AUS, etc
- 2) avoid high storage pressures } CIC preferred in most

What is Tethered cord syndrome (TCS)?

- stretch-induced functional disorder of the SC
- due to an anchored caudal end by inelastic structures } **often presents at growth spurts**
- symptoms } back pain, leg weakness, foot deformity, scoliosis, sensory loss, bowel dysfxn, lower urinary tract dysfunction
 - **change in or new neurologic symptoms**
- occurs in **3-15% of patients with MMC**
- NO TYPICAL UDS FINDINGS } irritative voiding symptoms, incontinence, retention
 - } **detrusor overactivity most common UDS finding**
- post-op UDS improves only in ~30%

What are the most common causes of tethered cord? }} “Scar Fixed To Bone”

- **Scar** from prior Sx
- Fibrous or fibroadipose Filum terminale
- Tumour
- Bony septum

What are the lower urinary tract features of TABES DORSALIS and PERNICIOUS ANEMIA?

→ “sensory neurogenic bladder”

- 1) clinical
 - **retention**
 - PVRs
- 2) UDS
 - **impaired detrusor contractility**
 - synergic sphincters
 - **loss of sensation**
 - N compliance

What are the lower urinary tract features of POLIOMYELITIS?

→ voiding dysfunction is a typical “motor neurogenic bladder”

- 1) clinical
 - retention
- 2) UDS
 - detrusor areflexia
 - intact sensation

DISEASE DISTAL TO THE SPINAL CORD

What are the lower urinary tract features of **LUMBAR DISK DISEASE**?

- sacral segments of SC are at level of L1 & L2 vertebral bodies
- most disk protrusions compress spinal roots in L4-L5 or L5-S1 vertebral interspaces
- **majority do not have voiding dysfunction } Normal UDS**
- 1) clinical
 - reflex & sensory loss consistent with nerve root compression
 - **sensory loss in perianal area (S2-S4) and lateral foot (S1-S2)**
 - **retention**
- 2) UDS
 - **detrusor areflexia** } can occasionally see detrusor overactivity
 - **competent, nonrelaxing smooth sphincter**
 - **synergic striated sphincter**
 - **N compliance**

What are the goals of management of voiding dysfunction associated w/ **LUMBAR DISK DISEASE**?

- laminectomy } essential to do pre-laminectomy UDS
 - may not improve voiding dysfunction
 - may in fact develop voiding dysfunction } detrusor overactivity, detrusor areflexia

What are the lower urinary tract features of **RADICAL PELVIC SURGERY**?

- most common after APR (20-70%), radical hysterectomy (16-80%), LAR (20-25%), & proctocolectomy (10-20%)
- voiding dysfunction probably lower now } nerve-sparing
- type of voiding dysfunction depends on specific nerves involved, degree of injury, and any pattern of reinnervation or altered innervation that develops over time
- **voiding dysfunction permanent in 15-20%**
- 1) clinical
 - **retention**
 - **SUI**
- 2) UDS
 - **impaired detrusor contractility or detrusor areflexia**
 - **open smooth sphincter**
 - **fixed EUS** } loss of voluntary control
 - **↓'d compliance** } may have N compliance

What are the causes of voiding dysfunction post-radical pelvic surgery?

- 1) denervation or neurologic decentralization
- 2) tethering of nerves or encasement in scar
- 3) direct bladder or urethral trauma
- 4) bladder devascularization

What are the goals of management of voiding dysfunction assoc'd w/ **RADICAL PELVIC SX**?

- **storage failure + emptying failure**
- **avoid irreversible Rx as voiding function improves with time**
- 1) maintain low pressure storage
- 2) facilitate emptying } CIC

What are the lower urinary tract features of **SPINAL STENOSIS**?

- narrowing of spinal canal, nerve root canals, or intervertebral foramina
- congenital, developmental, or acquired
- **UDS findings are dependent on level and amount of SC or nerve root damage**
- treatment based on UDS
- decompressive laminectomy improves voiding dysfunction in ~50%

What are the lower urinary tract features of **CAUDA EQUINA SYNDROME**?

- saddle anesthesia + loss of voluntary anal & urethral sphincter control + loss of sexual responsiveness
- causes } severe central posterior disk protrusion
- } any other spinal canal pathology (eg SC tumour, mets, spinal stenosis, etc)

1) clinical

- **urinary retention**

2) UDS

- **acocontractile detrusor**
- **inactive sphincter**
- **no bladder sensation**

needs emergency decompression

→ presence of leg symptoms often means too late (irreversible damage done)

What are the lower urinary tract features of **HERPES ZOSTER VIRUS INFECTION**?

- invasion of sacral dorsal root ganglia and posterior nerve roots
- voiding dysfunction may arise weeks after other primary viral manifestations
- voiding dysfunction only seen in ~25%
- 3 main types
 - 1) herpetic cystitis } dysuria, frequency, retention, hematuria, pyuria
 - 2) neuritis associated } urinary retention with detrusor areflexia
 - 2) myelitis associated } urinary incontinence with detrusor overactivity
- spontaneous resolution occurs in 1-2 months**

What is Elsberg syndrome?

- urinary retention + anogenital HSV infection + bilateral sacral nerve root involvement + sphincteric incontinence + CSF pleocytosis
- voiding dysfunction is transient

What are the lower urinary tract features of **DIABETES MELLITUS**?

- **voiding dysfunction occurs in 5-60%**
- related to peripheral & autonomic neuropathy } **affects sensory afferents 1st** but also affects motor
- 1) clinical
 - **low flow rates**
 - **retention (PVR)**
- 2) UDS
 - **variable detrusor function**
 - **impaired contractility, overactivity or areflexia**
 - end-stage diabetic bladders classically have decreased contractility
 - **synergic sphincter activity**
 - **N or increased compliance**
 - **impaired sensation**

What are the lower urinary tract features of **GUILLAIN-BARRE SYNDROME (GBS)**?

- inflammatory demyelinating disorder of peripheral somatic & autonomic nerves
- triggered by a preceding bacterial or viral infection (eg URTI, gastroenteritis, etc)
 - immune response directed at pathogen cross-reacts with neural tissues
- rapidly evolving symmetrical limb weakness, loss of DTRs, absent or mild sensory signs, and variable autonomic dysfunctions
 - limb weakness starts with lower limbs and spreads to upper limbs
 - can get HTN, hypoTN, cardiac arrhythmias
- resolution of paralysis usually occurs over wks to months
 - plasmapheresis +/- IVIG + supportive care
 - 5-10% mortality rate
- **voiding dysfunction occurs in 25-80%**
- **variable symptoms**
 - **retention**
 - **urgency, nocturia, urge incontinence**
 - **SUI**

MISCELLANEOUS NEUROLOGIC DISEASES CAUSING VOIDING DYSFUNCTION

What are some other neurologic disease associated with voiding dysfunction?

- Lyme disease } encephalopathy OR polyneuropathy OR leukoencephalitis (spirochete)
→ detrusor overactivity OR detrusor areflexia
- Hereditary Spastic Paraplegia } genetic demyelination disease presenting w/ leg weakness
→ detrusor overactivity OR impaired detrusor contractility
- Tropical Spastic Paraparesis } SC myelopathy caused by HTLV-1 presenting w/ back pain & leg weakness
→ detrusor overactivity OR detrusor areflexia
- AIDS } HIV infection can affect central & peripheral nerves
→ detrusor areflexia OR detrusor overactivity OR impaired detrusor contractility
- acute disseminated encephalomyelitis } multifocal inflammatory demyelinating disease
→ detrusor overactivity OR detrusor areflexia
- syringomyelia } chronic SC disease with dissociated sensory loss and brachial amyotrophy
→ detrusor overactivity OR detrusor areflexia
- schistosomal myelopathy } infiltration of bladder smooth muscle can cause BN obstruction & impaired contractility
} can rarely infiltrate SC
→ detrusor overactivity OR detrusor areflexia
- SLE } widespread inflammatory changes in small vessels and connective tissue
→ detrusor overactivity OR impaired detrusor contractility
- reflex sympathetic dystrophy } severe pain + autonomic changes associated with trauma
→ detrusor overactivity OR detrusor areflexia
- amyloidosis
- adult polyglucosan body disease
- neurofibromatosis
- spinal muscular atrophy
- Duchenne muscular dystrophy
- familial dysautonomia

MISCELLANEOUS CONDITIONS DEFINITELY, PROBABLY, OR POSSIBLY RELATED TO NEUROMUSCULAR DYSFUNCTION

What are the potential causes of DESD?

- **should only exist in patients with abN pathway between sacral SC and brain stem PMC**
- “SMCS - T”
- Suprasacral SCI
- MS (30-65%)
- Cerebral palsy (25%)
- Spina bifida (10%)
- Transverse myelitis

What are the 3 main types of DESD?

- 1) type 1 } concomitant increase in Pdet and EMG activity
} EUS suddenly relaxes at peak detrusor contraction
→ get unobstructed voiding
- 2) type 2 } sporadic contractions of EUS throughout detrusor contraction
- 3) type 3 } crescendo-decrescendo pattern of EUS contraction
→ obstruction throughout entire detrusor contraction

What are potential causes of pseudodyssynergia?

→ **not all simultaneous increases in Pdet and EMG activity indicates true DESD**

- abdominal straining to initiate or augment bladder contraction
- abdominal straining in response to discomfort
- attempted inhibition of bladder contraction that is involuntary or uncomfortable
- Parkinson's disease } actually slow rigid, akinetic EUS

What are the potential complications related to DESD?

→ **without proper treatment, >50% of men will develop significant complications**

- VUR
 - upper tract deterioration
 - stones
 - infections
 - ureterovesical obstruction
- } **complications much less common in F**

What are the treatment options for DESD?

→ goal is to lessen the abN EUS activity or to circumvent it

→ meds used mainly to control detrusor overactivity } not good for relaxing EUS

- 1) CIC
- 2) sphincterotomy
- 3) stent across EUS
- 4) botox injection into EUS
- 5) continuous catheterization (urethral, S/P, etc)
- 6) urinary diversion

What are the indications for sphincterotomy? }}} "A DUCHI?"

- Autonomic dysreflexia due to DSD
- **DESD**
- Upper tract deterioration risk in high risk patients (DLPP >40 cm H₂O)
- **CIC** difficulties
- **H**igh pressure voiding with severe hydronephrosis or VUR
- **I**ndependence of patient

List causes of late failure of sphincterotomy.

- incomplete sphincterotomy
- fibrosis at sphincterotomy site
- change in detrusor function
- development of BOO from BPH
- change in neuro status (eg new onset smooth sphincter DSD)
- BN contracture

How does Botulinum toxin work? **(AUA Update #15 - 2008)**

→ single chain polypeptide with molecular weight of 150 kDa

→ **prevents release of acetylcholine from pre-synaptic nerve terminal in NMJ**

- toxin binds to and cleaves cytosolic translocation protein (SNARE/SNAP-25), preventing vesicle with NTs from fusing with plasma membrane
- prevention of the release of NTs from the pre-synaptic nerve terminal results in paralytic effect

List potential GU applications of Botulinum toxin. **(AUA Update #15 - 2008)**

- neurogenic detrusor overactivity (100-300 units)
- idiopathic detrusor overactivity (100-300 units)
- IC/Painful Bladder syndrome
- Chronic Pelvic Pain Syndrome (CPPS) (100-200 units) → transvaginal or perineal
- BPH/tight BN (100-200 units) → transrectal or perineal
- DESD (50-200 units) → transurethral or perineal

List contraindications to Botulinum toxin injections. **(AUA Update #15 – 2008) }}** “BLAME Poison”

- Breast feeding
- Lou Gehrig’s disease (ALS)
- Aminoglycoside use (concomitant)
- Myasthenia gravis
- Eaton-Lambert syndrome
- Pregnancy

What is dysfunctional voiding?

- aka non-neurogenic neurogenic bladder, Hinman syndrome, occult neuropathic bladder
- appears as involuntary obstruction at level of EUS w/o any demonstrable neurologic disease
- difficult to prove on UDS alone
- need Hx, uroflowmetry, isolated Pdet measurements, pelvic floor EMG activity

What is bladder neck dysfunction?

- incomplete BN opening during voluntary or involuntary voiding
- non-neurogenic condition found almost exclusively in young and middle-aged men
 - also can refer to smooth sphincter dyssynergia associated with autonomic dysreflexia
- long-standing obstructive and irritative symptoms
- often given incorrect Dx of psychogenic voiding dysfunction
- N DRE + negligible PVR, + N endoscopic bladder appearance
- BN obstruction demonstrated on video UDS, VCUG, or micturitional UPP
- if BPH develops with age, they get double obstruction } “trapped prostate”
- Rx → α -blockers
- TUIBN (best results)

What is the DDx of BN dysfunction?

- anatomic BN contracture
- BPH
- dysfunctional voiding
- prostatitis
- neurogenic dysfunction
- low pressure/low flow

What is low pressure/low flow voiding (“bashful bladder”)?

- either due to decompensating detrusor OR as part of DHIC syndrome (elderly)
- occurs in young men } frequency, hesitancy (especially in public), and poor stream
- usually no identifiable abnormality on cysto
- Rx → behavioural modification program
- limited role for empirical meds & surgery

What are the causes of BOO in women?

- uncommon
- obstruction between BN and distal urethra in presence of sustained detrusor contraction
 - which is usually associated with reduced or delayed urine flow rate
- primary BN obstruction (female version of non-neurogenic BN dysfunction in males)
- dysfunctional voiding
- cystocele
- obstruction from prior incontinence surgery
- urethral stricture
- uterine prolapse
- urethral diverticulum
- rectocele

What are the potential causes of urinary retention in women?

- 1) neurologic
- 2) pharmacologic
- 3) anatomic
- 4) myopathic
- 5) functional
- 6) psychogenic

What is Fowler Syndrome?

→ **urinary retention in young F with no overt neurologic disease**

- capacity >1L with no urge sensation required for diagnosis
- UDS shows detrusor acontractility
- evidence of abN EMG } complex repetitive discharges + decelerating bursts
- } impairs sphincter relaxation
- **PCOS is common**

Rx → hormonal manipulation, meds, botox injections into sphincter not beneficial in most
 → highly responsive to neuromodulation (~70% success rate)

List potential causes of post-op urinary retention (**CHART**)?

→ occurs in 5-25%

- | | |
|--|---|
| 1) traumatic catheter insertion | 5) ↑'d outlet resistance |
| 2) bladder over-distension | 6) ↓'d micturition reflex activity |
| 3) diminished awareness of bladder sensation | 7) nociceptive inhibitory reflex |
| 4) ↓'d bladder contractility | 8) pre-existent outlet pathology (eg BPH) |

List some other diseases associated with voiding dysfunction.

Disease	Features	Other
hyperT4	<ul style="list-style-type: none"> - reduced flow rates - PVRs + retention - <u>increased EMG activity during voiding</u> 	<ul style="list-style-type: none"> - more common in F - resolves after resolution of <u>hyperT4</u>
schizophrenia	<ul style="list-style-type: none"> - overactivity 	<ul style="list-style-type: none"> - usually have hx of childhood voiding dysfunction (<u>incontinence, bedwetting</u>)
gastroparesis	<ul style="list-style-type: none"> - impaired contractility <li style="padding-left: 20px;">+/- poor sensation 	
myasthenia gravis	<ul style="list-style-type: none"> - overactivity OR areflexia 	
scleroderma	<ul style="list-style-type: none"> - impaired contractility OR areflexia 	<ul style="list-style-type: none"> - fibrosis of skin, abN small arteries, involvement of GI, <u>heart, lungs, kidney</u>
Ehler-Danlos	<ul style="list-style-type: none"> - impaired contractility - large capacity, PVRs - <u>associated w/ bladder tics</u> 	<ul style="list-style-type: none"> - fragility & hyperextensibility of skin, joint laxity
myotonic dystrophy	<ul style="list-style-type: none"> - no strict pattern (overactivity to areflexia) 	<ul style="list-style-type: none"> - distal muscle atrophy, cataracts, endocrine issues, retardation, testis atrophy, abN cardiac rhythms

What is Isaac's syndrome?

- rare neurologic disorder characterized by continuous muscle contraction + fasciculations + myokymia + excessive sweating + elevated creatinine kinase
- secondary to Ab's against K channels on peripheral nerves
- associated with peripheral neuropathy, autoimmune diseases, malignancies, and endocrine disorders
- retention from spasm of periurethral striated sphincter
- Rx → resolves with Rx (plasmapheresis + skeletal muscle relaxants)

What is Wernicke's encephalopathy?

- rare condition caused by thiamine deficiency (Vit B1) in both alcoholics & non-alcoholics
- see periventricular lesions at level of 3rd and 4th ventricles
- cardiovascular & neurologic involvement
- involuntary detrusor contractions
 - can also see ED
- Rx → thiamine replacement

What are the affects of RADS on voiding function?

- early reaction phase at 4-6 weeks } mostly storage symptoms
- } reduced volumes, reduced capacity, reduced compliance
- later symptoms tend to be progressive & intractable } mostly storage symptoms

How does a previously defunctionalized bladder work after being reclaimed?

- previously N bladder will show decreased capacity + involuntary contractions +/- poor compliance
- rehabilitation is possible } cycling with progressively increasing volumes
- renal Tx into defunctionalized bladder successful only if capacity is >100mL & voiding pressure is <100 cm/H₂O

TREATMENT OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION: OVERVIEW

What are the general goals of management for voiding dysfunction (CHART)?

- must always take into account patient wishes and practicality
- always start with least invasive, most reversible treatments
- 1) upper tract preservation or improvement
- 2) absence or control of infection
- 3) adequate storage at low intravesical pressures
- 4) adequate emptying at low intravesical pressures
- 5) adequate control
- 6) no catheter or stoma
- 7) social acceptability and adaptability
- 8) vocational acceptability and adaptability

What are some patient factors to consider in choosing Rx?

- 1) prognosis of underlying disease (especially if progressive or malignant)
- 2) general health
- 3) limiting factors (inability to perform certain tasks eg hand dexterity)
- 4) mental status
- 5) motivation
- 6) desire to remain catheter or appliance free
- 7) desire to avoid surgery
- 8) sexual activity status
- 9) reliability
- 10) educability
- 11) psychosocial environment, interest, reliability, and cooperation of family
- 12) economic resources

List indications to change or augment a given Rx (CHART).

- 1) upper tract deterioration
- 2) recurrent sepsis or fever of urinary tract origin
- 3) lower tract deterioration
- 4) inadequate storage (volumes and pressures)
- 5) inadequate emptying (volumes and pressures)
- 6) inadequate control
- 7) unacceptable side effects
- 8) skin changes secondary to incontinence or collecting device

MISCELLANEOUS

What is the recommended follow-up of SCI patients with urologic issues? (includes AUA Update #25 – 2008)

- f/u q1yr for first 5-10yrs after injury } if well, q2yrs after that
 → upper & lower tract evaluation } AXR, renal U/S or renal scan
 } UDS
- cystoscopy q1yr for those with indwelling catheters starting at ~8yrs

List options for management of neurogenic detrusor overactivity. (AUA Update #25 – 2008)

- anti-cholinergics (1st line) +/- intravesical Rx (eg resiniferatoxin)
- botulinum toxin injections
- neuromodulation
- bladder augmentation

List benefits of CIC over indwelling catheters. (AUA Update #25 – 2008)

- improved QOL
- **facilitates sexual activity**
- **↓'d risk of pyelonephritis**
- lower risk of stones (renal, bladder, etc)
- maintenance of bladder compliance (>80% loss with indwelling)
- ↓'d risk of prostatitis, epididymitis, orchitis, Fournier's gangrene
- ↓'d risk of urethral strictures
- ↓'d risk of traumatic hypospadias (M & F) and "lead-pipe" urethra (F)

List disadvantages of sphincterotomy + external collection device as a mgt strategy. (AUA Update #25 – 2008)

- all ablative sphincterotomy techniques not ideal
- not feasible in F
- difficult in patients with small penis, large S/P fat pad, etc
- condom catheters have similar risk of infection as indwelling catheters
- skin breakdown

Chapter #60 – Urinary Incontinence

DEFINITION AND CLASSIFICATION OF URINARY INCONTINENCE

What is the ICS definition of urinary incontinence?

- the complaint of any involuntary loss of urine
- should also mention type, severity, precipitating factors, social impact, effect on hygiene and QOL, measures used to contain leakage, desire for help
- can be Dx'd by clinical signs and by UDS

What are the 3 main types of incontinence?

- 1) stress } involuntary leakage with exertion, sneezing, coughing, etc
→ UDS: leakage with increases in Pabdo in the absence of detrusor contraction
- 2) urgency } involuntary leakage accompanied by or immediately preceded by urgency
→ UDS: detrusor overactivity causing leakage
- 3) mixed } involuntary leakage assoc'd w/ urgency & also w/ exertion, sneezing, coughing, etc

List other types of incontinence.

- unconscious incontinence } involuntary loss of urine WITHOUT stress or urgency
- continuous incontinence } continuous leakage
- nocturnal enuresis } loss of urine during sleep
- post-micturition dribble } involuntary loss of urine immediately after voiding
- overflow incontinence } leakage of urine associated with retention
- extraurethral incontinence } urine leakage through channels others than the urethra (eg fistula, ectopic ureter)

EPIDEMIOLOGY OF URINARY INCONTINENCE

What are the RFs for urinary incontinence?

- predisposing
 - sex (female)
 - genetic predisposition
 - race (whites > blacks)
 - anatomic/neurologic factors } previous vaginal delivery (obstructed labour), RADs, pelvic nerve/muscle damage, etc
- promoting
 - obesity
 - poor nutrition
 - smoking
 - activity level
 - toilet habits
 - fluid intake
 - pregnancy } associated with 30-60% prevalence of incontinence
- decompensating
 - aging
 - physical and mental well-being
 - environment
 - meds

How common is urinary incontinence in WOMEN?

- 5-20% prevalence
- increasing prevalence with age
- prevalence of severe incontinence is 5-10%
- **overall, SUI is most common in F (~50%),** then mixed (~30%) and urge (~20%)
- proportion of types of incontinence varies with age
 - **SUI is most common in young & middle-aged F**
 - **mixed incontinence is most common in older F**

What is the influence of menopause on urinary incontinence rates?

- menopause may be associated with increased risk of incontinence } **CONTROVERSIAL**
- hormone replacement **DOES NOT** improve or prevent incontinence

How common is urinary incontinence in MEN?

- 3-10% prevalence
 - about 1/2 as prevalent as women
- increasing prevalence with age
 - rises more steadily than women
- **overall, urge incontinence is most common (40-80%),** then mixed (10-30%) and stress (<10%)
 - SUI is the least common type unless associated with RP, neurologic injury, or trauma

CONTINENCE AND THE PHYSIOLOGY OF MICTURITION

Which properties of the bladder & sphincter promote continence?

- | | |
|------------------|--------------------|
| → bladder | → sphincter |
| - accommodation | - coaptation |
| - compliance | - compression |
| - capacity | - anatomic support |
| - neural control | - neural control |

From an anatomic perspective, what are the causes of urinary incontinence?

- 1) bladder problem
 - detrusor overactivity
 - impaired compliance
- 2) sphincter dysfunction
 - ISD
 - urethral support defect (hypermobility)

What neural pathways are required for normal storage of urine?

- 1) spinal reflex mechanisms that activate sympathetic & somatic pathways to bladder & outlet
 - distension stimulates sympathetics & pudendal outflow (guarding reflex)
 - relaxation of detrusor smooth muscle
 - contraction of sphincters
 - inhibition of parasympathetics
- 2) tonic inhibitory mechanisms in brain suppress parasympathetic excitatory outflow to bladder

What neural pathways are required for normal voiding?

- 1) voluntary control of micturition reflex organized in PMC (Barrington's nucleus)
 - inhibition of spinal guarding reflex
 - activation of parasympathetics to urethra & bladder
- 2) integration and modulation by the parasympathetic & somatic components of the sacral spinal cord with the thoracolumbar sympathetics
 - contraction of detrusor smooth muscle
 - relaxation of sphincters

What are the 5 principles underlying the function of the urethral sphincter?

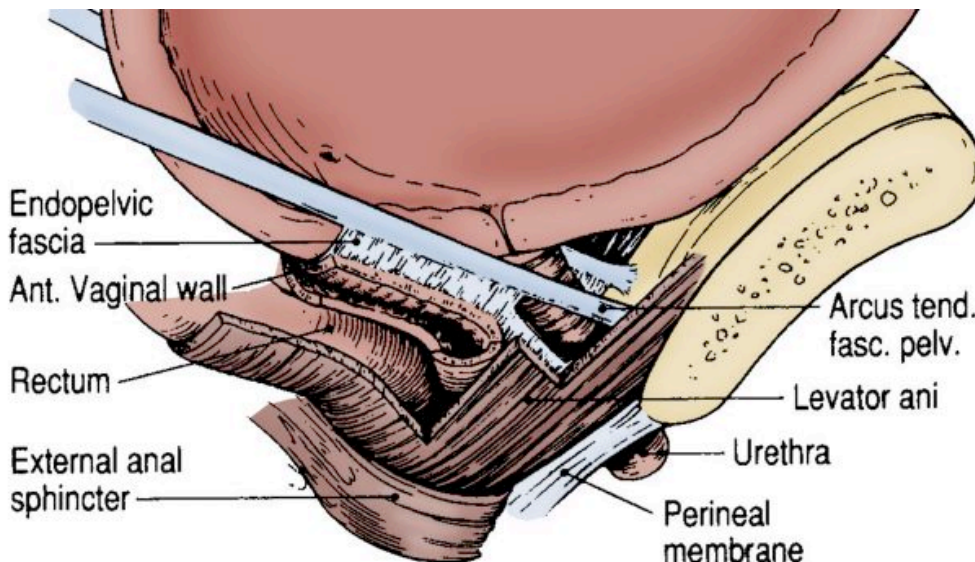
- 1) watertight apposition of urethral lumen
- 2) compression of the wall around the lumen
- 3) structural support to keep proximal urethra from moving during increases in pressure
- 4) a means of compensating for abdominal pressure changes (pressure transmission)
- 5) neural control

What are the 5 factors involved in external compression of the urethral lumen?

- 1) smooth & striated muscle tone
- 2) phasic contractions of the smooth & striated musculature
- 3) elastic & viscoelastic properties of the extracellular matrix
- 4) mechanical factors related to transmission of abdominal pressure
- 5) structural (anatomic) support of the posterior urethral wall

What is DeLancey's "hammock theory" behind the pathophysiology of SUI?

- 1) increased Pabdo compresses urethra closed against a hammock-like musculofascial layer on which the bladder and urethra rest
→ stability of supporting layer determines stress incontinence NOT position of urethra
 - 2) stability of urethra determined by anterior vaginal wall and its connections to the levator ani muscles and the arcus tendineus fascia (pubic bone to ischial spine)
→ endopelvic fascia + pubocervical fascia
→ even in setting of urethral hypermobility, continence can still be maintained if this supporting layer establishes stability at a lower level
- **primary goal of surgery for sphincteric incontinence in women is to provide backboard against which BN & proximal urethra can be compressed during increases in Pabd**
- **midurethral complex also plays significant role**
→ pubourethral ligaments attach anterior midurethra to inferior aspect of pubic bone
→ pubourethralis muscle (levator ani complex) forms sling around proximal urethra
- **midurethra is most likely the most important zone of continence**



→ DELANCEY'S HAMMOCK THEORY OF STRESS INCONTINENCE

What is McGuire's ISD theory behind the pathophysiology of stress incontinence?

- 1) ISD is an intrinsic malfunction of the urethral sphincter, regardless of its anatomic position
 - open BN and proximal urethra at rest
 - current thought is that all pts with sphincteric incontinence have some degree of ISD
 - many women with hypermobility are continent
 - N urethra remains closed no matter the degree of rotational descent
 - 2) ISD can and often does co-exist with urethral hypermobility
- SUI should be characterized by 1) degree of urethral mobility and 2) sphincter strength (VLPP)**

What are the 2 functional parts of the male urinary sphincter?

- 1) proximal urethral sphincter } BN, prostate, and prostatic urethra (to verumontanum)
 - } innervated by parasympathetics from pelvic nerve
- 2) distal urethral sphincter } prostatomembranous urethra, EUS, levator ani complex
 - } EUS is mainly slow-twitch (type 1) skeletal fibers
 - } levator ani complex are fast-twitch (type 2) skeletal fibers

What structures provide support for the male EUS?

- 1) urethral plate } ventral support that is also origin of rectourethralis muscle
- 2) puboprostatic ligaments } dorsal support that fuse with EUS

ETIOLOGY AND PATHOPHYSIOLOGY OF URINARY INCONTINENCE

What are the causes of urinary incontinence (CHART)?

- 1) urethral
 - abN bladder } detrusor overactivity
 - } low bladder compliance
 - } impaired contractility
 - abN sphincter } ISD
 - (bladder outlet) } urethral hypermobility
 - } anatomic destruction (eg post-RP, trauma, etc)
 - } outlet obstruction
 - combination of both
- 2) extraurethral
 - fistula
 - ectopic ureter

Abnormal Bladder

What are the causes of detrusor overactivity (CHART)?

- 1) Idiopathic detrusor overactivity
- 2) Neurogenic detrusor overactivity
 - supraspinal lesions
 - stroke/CVA
 - Parkinson's disease
 - hydrocephalus
 - brain tumours
 - traumatic brain injury
 - MS
 - suprasacral spinal lesions (often see DESD)
 - SCI or SC tumour
 - MS
 - myelodysplasia
 - transverse myelitis
 - DM
- 3) Non-neurogenic detrusor overactivity
 - UTI
 - BOO
 - M } BPH, BN strictures
 - F } pelvic organ prolapse, urethral tic, post-incontinence Sx, strictures, primary BN
 - bladder tumour
 - bladder stone or FB
 - aging

How do you classify detrusor overactivity?

- 1) in relation to neurologic disease } neurogenic detrusor overactivity
VS idiopathic detrusor overactivity
- 2) phasic, terminal, both } terminal detrusor overactivity resembles N micturition reflex except that it is involuntary
} phasic detrusor overactivity is intermittent (may not cause incontinence)

What are the 4 types of OAB based on UDS?

- 1) type 1 } **symptoms** but no involuntary detrusor contractions seen on UDS
- 2) type 2 } involuntary detrusor contractions present but patient able to voluntarily contract sphincter, **able to prevent incontinence & abort contraction**
- 3) type 3 } involuntary detrusor contractions present and patient able to voluntarily contract sphincter and **momentarily prevent incontinence but unable to abort contraction; once sphincter fatigues, incontinence occurs**
- 4) type 4 } involuntary detrusor contractions present but patient **can't voluntarily contract or abort contraction** and simply voids involuntarily

What are the causes of low bladder compliance?

- **compliance less important than actual bladder pressure during filling**
- **sustained detrusor pressure >40 cm H₂O during storage, regardless of volume, can lead to upper tract deterioration**
- 1) changes in elastic & viscoelastic properties of the bladder
 - primarily due to changes in ECM
 - a) collagens (type 1 and 3 most important) } ↑'d type 3 assoc'd w/ poor compliance
 - b) elastins } ↓'d elastin expression associated with poor compliance
 - c) proteoglycans
 - d) glycoproteins
- 2) changes in detrusor muscle tone
 - neuroplasticity
- 3) combination of the two

What is the classification of low bladder compliance (CHART)?

- 1) **neurogenic ("SIMS")**
 - sacral SCI or lesion
 - iatrogenic } APR, radical hysterectomy, etc
 - multi-system atrophy } Shy-Drager syndrome
 - spina bifida
- 2) **non-neurogenic (see increased collagen)**
 - TB cystitis
 - radiation cystitis
 - interstitial cystitis
 - chronic indwelling catheter
 - BOO

Abnormal Sphincter

What are the potential causes of ISD in women?

- 1) previous urethral or periurethral surgery
 - eg anti-incontinence, urethral diverticulectomy, radical hysterectomy, APR, etc
 - from periurethral fibrosis, scarring, or denervation
- 2) neurologic insult
 - eg sacral neurologic lesions } somatics, sympathetics
- 3) aging
- 4) hypoestrogenic state

What are the potential causes of urethral hypermobility?

- pregnancy
- vaginal delivery
- pelvic surgery
- chronic abdominal straining (chronic cough, constipation)
- neurologic injury

What are the potential mechanisms by which vaginal delivery might lead to sphincteric damage & SUI?

- 1) injury to connective tissue support during delivery
- 2) vascular damage to pelvic structures due to compression by fetus
- 3) damage to pelvic nerves and/or muscles during delivery
- 4) direct injury to urinary tract during delivery

What are the RFs for pudendal nerve injury associated with vaginal delivery?

- would affect striated sphincter function
 - multips
 - forceps delivery
 - increased duration of 2nd stage of labour
 - epidural
 - 3rd degree perineal tear
 - high birth wt (>4kg)

How do you classify sphincteric incontinence?

- based on VUDS features with increased Pabdo/Valsalva
- type 0 } BN descent + BN closed at rest BUT NO LEAKAGE
- type 1 } BN descent ≤2cm + BN closed at rest + LEAKAGE
- type 2a } BN descent >2cm (below inferior margin of symphysis) + BN closed at rest + LEAKAGE
- type 2b } BN down at rest + BN closed at rest + LEAKAGE
- type 3 } BN down & open at rest + LEAKAGE

What are the potential causes of sphincteric abnormalities in men?

- 1) trauma
- 2) neurologic injury
- 3) RADs

DIAGNOSTIC EVALUATION

What is involved in the work-up of a patient with incontinence/pelvic organ prolapse?

- 1) History } characterize any incontinence
 - frequency, severity, type, degree of bother, effect on QOL, precipitants, previous treatment to date, pad use, etc
 - } **need to assess lower GU tract, bowel fxn, sexual fxn, & local symptoms**
 - LUTS } frequency, urgency, nocturia, weak stream, intermittency, straining, incomplete emptying
 - } hx of UTIs, AUR, hematuria, etc
 - anal incontinence, difficulty defecating/constipation
 - dyspareunia, decreased desire (most common)
 - local symptoms include vaginal pressure/heaviness, vaginal/perineal pain, low back pain, abdo pressure or pain, palpable bulge/mass
 - } **voiding diary (3 days optimal), fluid intake habits, pad tests, questionnaires**
 - } ask about RFs for incontinence + r/o causes of transient incontinence
 - vaginal deliveries, obese, poor nutrition, smoker, activity level, etc
 - DIAPPERS
 - } PMHx (eg stroke, MS, SCI, RADs, menses, etc)
 - } PSHx (APR, hysterectomy, RP, etc)
 - } meds, allergies, drugs
- 2) P/E } neurologic exam (gait, perineal sensation, bulbocavernosus reflex, cognitive status)
 - } abdo exam (distended bladder, masses, hernias, DRE, etc)
 - } female pelvic exam (vaginal atrophy, skin excoriation, vault exam, organ prolapse, pelvic floor muscle strength, cough test, Q-tip test, Marshall test, +/- dye tests)
 - **need to r/o prolapse associated w/ occult or masked SUI**
 - lithotomy and standing exams
 - if incontinence not demonstrable in lithotomy, repeat in standing position
 - Q-tip test = urethral hypermobility
 - Marshall test = anterior vaginal wall
 - **anterior, apical/middle, and posterior compartment**
 - also assess rectovaginal septum, perineal body, anal sphincter, pelvic floor muscles
- 3) routine lab tests } urinalysis, urine C&S, +/- cytology +/- serum creatinine
- 4) initial investigations } uroflow + PVR
- 5) (WHEN INDICATED) additional testing } cystoscopy + UDS + imaging + EMG
 - CMG } detrusor overactivity, low compliance, VLPP, DLPP
 - PFS } high pressure + low flow, low pressure + low flow
 - } BOOI >40 is obstruction [$P_{det}Q_{max} - 2(Q_{max})$]
 - } BCI <100 is poor contractility [$P_{det}Q_{max} + 5(Q_{max})$]

What are the causes of transient incontinence (CHART)? } } } “DIAPPERS”

- | | | |
|--|-----------|---------------------------------------|
| <ul style="list-style-type: none">- Delirium- Infection (symptomatic UTI)- Atrophic vaginitis/urethritis- Psychological (depression, neurosis)- Pharmacologic (meds)- Excess urine production- Restricted mobility- Stool impaction | / / / / / | <p>seen especially in the elderly</p> |
|--|-----------|---------------------------------------|

What is the significance of the bulbocavernosus reflex?

- looking for contraction of anal sphincter & perineal muscles w/ sudden squeeze of glans/clitoris or pulling of foley balloon
- absence in men almost always associated with neurologic lesion
- absent in up to ~30% of normal women

What is the definition of a positive Q-tip test (ICS)?

- hypermobility = resting or straining angle **>30 degrees off horizontal**

What is the definition of a +ve pad test (ICS)?

- 1hr test } >1g in 1hr
- 24hr test } >1.3g to 8g (no consensus) over 24hrs

What is the role of cystourethroscopy in the incontinence patient?

- 1) assessment of female sphincter unit for coaptation and to r/o diverticula, etc
- 2) assess bladder for concomitant conditions
- 3) r/o extraurethral cause of incontinence
- 4) intra-op endoscopy during correction of stress incontinence
- 5) post-RP evaluation of anastomosis
- 6) assessment of bladder outlet in men

What are the goals of UDS in the incontinence patient?

- 1) determine if incontinence is due to bladder problem or urethral problem
- 2) determine if storage problem only or if there is also emptying problem
- 3) assess for RFs associated with upper tract deterioration
 - DESD, low compliance, high storage pressures, VUR secondary to high Pves

What parameters can be measured with a simple “eyeball” UDS?

- can be done at time of cystoscopy (15-20cm above patient)
- PVR
- bladder sensation
- bladder compliance
- bladder capacity
- involuntary detrusor contractions
- urethral competence

List indications for additional testing (UDS, cysto, etc) in incontinence/prolapse (CHART).

- hematuria without UTI
- abN PVR
- complex presentation where more precise information is desired
- patients with known or suspected voiding phase dysfunction that may affect Rx
- patients with known or suspected neurologic disorder that may affect bladder or sphincter
- unable to demonstrate incontinence clinically despite patient complaints
- Rx with potential for significant morbidity
- failure of empiric Rx
- hx of anti-incontinence or lower urinary tract reconstructive surgery
- hx of radical pelvic surgery (APR, etc)
- hx of high dose RADs to pelvis
- hx of urogenital or pelvic surgery + symptomatic pelvic prolapse

What is the role of UPP in the incontinent patient?

→ **limited role in incontinence**

- higher risk of stress incontinence associated with functional urethral length <3cm and MUCP <40 cm H₂O
- can't discriminate urethral incompetence from other disorders
- can't provide a measure of severity
- can't reliably predict surgical success

Table 60-6 -- Questionnaires Highly Recommended by the Third International Consultation on Incontinence for the Evaluation of Urinary Incontinence (UI), Lower Urinary Tract Symptoms (LUTS), and Overactive Bladder (OAB)

<i>I. Symptoms of UI</i>	
A. Women	Urogenital Distress Inventory (UDI) (Shumaker et al, 1994)
	UDI-6 (Ubersax et al, 1995)
	Incontinence Severity Index (Sandvik et al, 1993)
	BFLUTS (Jackson et al, 1996)
B. Men	ISCMale (Donovan et al, 1996)
	DAN-PSS (Hald et al, 1991)
<i>II. Quality of Life Impact of UI</i>	
A. Men and women	I-QOL (Wagner et al, 1996 ; Patrick et al, 1999)
	SEAPI-QMN (Raz and Erickson, 1992 ; Stothers, 2004)
B. Women	King's Health Questionnaire (Kelleher et al, 1997)
	Incontinence Impact Questionnaire (Wyman et al, 1987)
	IIQ-7 (Ubersax et al, 1995)
	Urinary Incontinence Severity Score (UISS) (Stach-Lempinen et al, 2004)
	CONTILIFE (Amarenco et al, 2003)
C. Men	None
<i>III. Combined Symptoms and Quality of Life Impact of UI</i>	
A. Men and women	ICIQ (Avery et al, 2004)
B. Women	Bristol Female LUTS-SF (Brookes et al, 2004)
	SUIQQ (Kulseng-Hanssen and Borstad, 2003)
C. Men	ICSMaleSF (Donovan et al, 1996)
<i>IV. Combined Symptoms and Quality of Life Impact of OAB</i>	
A. Men and women	OAB-q (Coyne et al, 2002)

From Donovan J, Bosch R, Gotoh M, et al: *Symptom and quality of life assessment*. In Abrams P, Cardozo L, Khoury S, Wein A (eds): *Incontinence (Edition 2005) 3rd International Consultation on Incontinence*. United Kingdom (UK), Health Publications, 2005, pp 519-584.

URINARY INCONTINENCE TREATMENT OVERVIEW

Table 60-8 -- Condition-Specific Treatments for Incontinence

Condition	Treatment
Detrusor overactivity	Treat underlying condition (e.g., UTI, bladder stone, urethral obstruction)
	Behavioral modification/lifestyle changes
	Pelvic floor muscle therapy
	Oral pharmacologic agents[*]
	Antimuscarinics
	Musculotropic relaxants
	Tricyclic antidepressants
	Intravesical agents[†]
	Oxybutynin
	Capsaicin
	Resiniferatoxin
	Botulinum toxin
	Neuromodulation
	Augmentation enterocystoplasty[*]
	Autoaugmentation[*]
	Denervation procedures
	Urinary diversion
Low bladder compliance	Oral pharmacologic agents[*]
	Antimuscarinics
	Musculotropic relaxants
	Tricyclic antidepressants
	Augmentation enterocystoplasty[*]
	Autoaugmentation[*]
	Denervation Procedures
Sphincteric dysfunction	Behavioral modification/lifestyle changes
	Pelvic floor muscle therapy
	Oral pharmacologic agents
	α -Adrenergic agonists
	Serotonin-norepinephrine reuptake inhibitors[‡]
	Urethral bulking agents
	Surgery
	Midurethral sling
	Pubovaginal sling
	Urethral/colposuspension
	Artificial urinary sphincter

* With or without intermittent self-catheterization.

† These treatments must be considered investigational and are "off label" in most countries.

‡ Duloxetine is not approved by all regulatory agencies worldwide, including the U.S. Food and Drug Administration for the treatment of stress incontinence.

What are the management options for incontinence caused by detrusor overactivity?

→ URGE INCONTINENCE

- first treat all remediable causes } eg UTI, urethral obstruction, bladder stone, FBs, bladder Ca, BPH, herniated lumbar disk, prolapse
 - **TURP improves OAB symptoms in 2/3 of men w/ BPH**
 - **urethrolisis improves OAB symptoms in ~70% of women w/ BOO due to anti-incontinence Sx**

→ CONSERVATIVE THERAPY

- 1) behaviour Rx } Bladder training (timed/scheduled voiding, urge inhibition techniques, etc)
 - } Education (anatomy & function)
 - } Habits (decrease caffeine intake, fluid restriction prn, decrease carbonated drinks, wt loss, improved bowel habits)
 - } Voiding diary
- 2) pelvic floor muscle training } Kegels, pelvic floor exercises
- 3) biofeedback
- 4) external devices } pessaries, urethral plugs, clamps, etc

→ PHARMACOLOGIC THERAPY

- 1) oral meds } antimuscarinics
 - most have partial efficacy (↑'d volume to 1st involuntary contraction, ↓ in amplitude, ↑ in capacity)
 - M3 is most important but there are 3-4x more M2 receptors in bladder
- } TCAs
 - imipramine } direct detrusor relaxant effects, sympathomimetic & central effects
- } muscolotropic relaxants
- 2) intravesical meds } oxybutynin
 - } capsaicin (block vanilloid receptors – C fiber afferents)
 - initial excitatory effect followed by prolonged desensitization
 - use limited by pain & hematuria post instillation
 - } resiniferatoxin (block vanilloid receptors – C fiber afferents)
 - 1000x more potent cf capsaicin but w/ no initial excitatory effect
 - } botox A (100-300 units)
 - inhibits acetylcholine release at presynaptic junction

→ SURGICAL THERAPY

- 1) neurologics
 - a) neurostim } induction of somatic afferent inhibition of sensory processing in SC
 - **S3 dorsal root**
 - } temporary lead trial and if +ve response (>50% improvement) then permanent neurostimulator implanted
 - mainly for non-neurogenics (2nd line Rx)
 - b) acupuncture
 - c) peripheral nerve stimulators } eg posterior tibial nerve
- 2) open surgery
 - a) augments } increases capacity & decreases detrusor overactivity
 - effective for neurogenic & non-neurogenic detrusor overactivity
 - many will need CIC afterwards
 - } autoaugmentation also an option
 - myotomy or myectomy creates mucosal bulge or pseudo-tic
 - poor results long-term
 - b) denervation } complete S2-4 rhizotomy, partial rhizotomy, subtrigonal phenol or EtOH injections, bladder transection + reattachment
 - poor long term results & ++ morbidity
 - **ABANDONED**
 - c) diversion } continent or incontinent
 - } may be preferred if overactivity or impaired compliance is 2° to RADs or in patients unable to catheterize through the urethra

What are some of the common anti-muscarinics agents used for detrusor overactivity (CHART)?

→ **grade A recommendation**

- oxybutynin (Ditropan – mixed action)
- tolterodine (Detrol)
- darifenacin (Enablex)
- solifenacin (Vesicare)
- trospium (Trosec/Sanctura)
- propiverine

→ grade B recommendations

- propantheline

→ grade C recommendation

- hyoscyamine

What are some common side effects of anti-muscarinics?

- dry mouth
- constipation
- blurred vision
- GI upset
- cognitive decline
- urinary retention
- supraventricular tachycardia
- skin rash

What are some potential complications of neuromodulations?

- pain at generator site
- pain at implant site
- lead migration
- revision
- infection
- skin irritation
- adverse changes in bowel/bladder function

List contraindications to sacral neurostimulation } } } “Trade Magdy PEPSI For Neurostim ”

- Tumour of SC
- Myogenic damage (acontractility)
- Peripheral nerve injury
- End-stage, small contracted bladder
- Pregnancy
- Sacral SCI
- Incapacitated patient (eg MR)
- Functional urinary incontinence
- Non-compliance

How does Botulinum toxin work? **(AUA Update #15 - 2008)**

- single chain polypeptide with molecular weight of 150 kDa
- **prevents release of acetylcholine from pre-synaptic nerve terminal in NMJ**
- toxin binds to & cleaves cytosolic translocation protein (SNARE/SNAP-25), preventing vesicle with NTs from fusing with plasma membrane
- prevention of the release of NTs from the pre-synaptic nerve terminal results in paralytic effect

List potential GU applications of Botulinum toxin. **(AUA Update #15 – 2008)**

- neurogenic detrusor overactivity (100-300 units)
- idiopathic detrusor overactivity (100-300 units)
- IC/Painful Bladder syndrome
- Chronic Pelvic Pain Syndrome (CPPS) (100-200 units) → transvaginal or perineal
- BPH/tight BN (100-200 units) → transrectal or perineal
- DESD (50-200 units) → transurethral or perineal

List contraindications to Botulinum toxin injections. **(AUA Update #15 – 2008)**

→ **“BLAME Poison”**

- Breastfeeding
- Lou Gherig disease (ALS)
- Aminoglycoside use (concomitant)
- Myasthenia gravis
- Eaton-Lambert syndrome
- Pregnancy

What are the principles of augmentation cystoplasty?

- 1) detubularize along anti-mesenteric border
- 2) reconfigure bowel segment into shape of a half-sphere
- 3) wide anastomosis between bowel and bladder
- 4) large bladder capacity must be achieved

What are the potential complications of augmentation cystoplasty?

→ metabolic

- 1) **G**rowth retardation
- 2) **D**rug metabolism abnormalities
- 3) **I**nfections (UTIs)
- 4) **V**itamin B12 deficiency
- 5) **E**lectrolyte abnormalities
- 6) **R**enal failure
- 7) **S**tones
- 8) **I**ntestinal problems
- 9) **O**steomalacia
- 10) **N**eoplasms
- 11) **S**ensorium alterations

→ mechanical

- bowel anastomotic leak
- SBO
- fistula
- atonic bladder
- delayed spontaneous bladder perforation +/- fistula
- refractory poor compliance/uninhibited contractions

What are the management options for incontinence caused by sphincteric dysfunction?

→ **STRESS INCONTINENCE**

➔ CONSERVATIVE THERAPY

- 1) behaviour Rx } Bladder training (timed/scheduled voiding, urge inhibition techniques, etc)
 } Education (anatomy & function)
 } Habits (decrease caffeine intake, fluid restriction prn, decrease carbonated drinks, wt loss, improved bowel habits)
 } Voiding diary
- 2) pelvic floor muscle training } Kegels, pelvic floor exercises
 → RCT shows PFMT is better than no treatment for SUI
 → no/minimal added benefit of biofeedback
- 3) biofeedback
- 4) external devices } pessaries, urethral plugs, clamps, etc

➔ PHARMACOLOGIC THERAPY

- 1) oral meds } α -agonists (increase urethral muscle tone eg ephedrine, PPA, midodrine)
 } \rightarrow only weak evidence showing they are better than placebo
 } SNRIs (eg duloxetine)
 } TCAs (eg imipramine)
- 2) topical meds } estrogen \rightarrow NO ROLE FOR SUI (possibly to improve tissue quality)

→ **SURGICAL THERAPY**

- 1) minimally invasive surgery
 - a) urethral bulking agents } collagen, hyaluronic acid/dextranomer (Zuidex/Deflux), PTFE, polydimethylsiloxane elastomer (Macroplastique)
→ short-duration of effect
 - b) PVS & midurethral slings
 - c) urethral culposuspension (open vs laparoscopic)
 - d) needle suspensions
 - e) AUS
 - f) vaginal anterior repair (anterior colporrhaphy)
- 2) open surgery
 - a) diversion } only considered for refractory cases with severe sphincteric damage

What are the potential side effects of α -agonists?

→ most are not uro-selective & so have common systemic side effects

- HTN
- palpitations
- H/A
- tremor
- sleep disturbances

How does correction of SUI affect other lower urinary tract symptoms?

- **surgical correction of SUI improves/cures urge incontinence in 60-80%**
- **~10% will develop de novo urge incontinence after surgical correction of SUI**
- **concomitant pelvic organ prolapse should be corrected at same time as SUI**

What factors determine the surgical option of choice for SUI?

- 1) underlying condition } degree of urethral mobility, VLPP
- 2) outcome data on various procedures
- 3) surgeon preference and expertise
- 4) patient-factors } age, comorbidities, desire for fast recovery vs complete success, avoidance of complications

What are the surgical options for management of SUI?

- 1) urethral bulking agents } poor long-term success
- 2) slings } most efficacious for long-term success
 - } PVS & midurethral
 - autologous fascia best material for PVS
 - midurethral slings (eg TVT, TVT-O, etc) are comparable
- 3) suspensions } transvaginal & retropubic (eg Marshall-Marchetti or Burch colposuspension)
 - retropubic better
- 4) sphincter prostheses } AUS
 - } good results as primary or re-do but higher morbidity
 - } abandoned (especially in women) for faster, easier, less invasive slings
- 5) diversion } last resort option for severe sphincteric damage

→ **newer slings comparable to old gold standard (PVS & retropubic suspension) } 80-95% success**

What are surgical options for male SUI?

- mainly in post-RP men } also for trauma or neurologic injury
- PFMT for all
- 1) urethral bulking agents } poor results
- 2) slings } passive external urethral compression
 - mainly for mild and moderate SUI only
 - poor outcomes for severe incontinence
- 3) AUS } gold standard with excellent success rates
- 4) diversion } last resort option
 - severe refractory sphincter dysfunction +/- RADs +/- strictures

Which patients would benefit from immediate surgery?

- significant associated organ prolapse (beyond hymen)
- highly motivated to be completely dry
- high levels of stress owing to lifestyle or occupation } low QOL
- severe SUI
- good pelvic floor function on initial examination

What are the RFs for post-RP urinary incontinence?

- patient factors
 - 1) **patient age**
 - 2) **pre-op voiding function**
 - 3) abN detrusor contractility
 - 4) prior TURP (controversial)
- disease factors
 - 5) higher stage
 - 6) **pre-op or post-op RADs**
 - 7) **surgical technique (NS vs non-NS)**
 - 8) surgeon experience
 - 9) excessive blood loss

Chapter #61 – Overactive Bladder

ETIOLOGY

What is the ICS definition of OAB (2002)?

→ **urgency, with or without urgency incontinence, usually with frequency & nocturia**

- urgency = complaint of sudden compelling desire to pass urine which is difficult to defer
- urgency incontinence = complaint of involuntary leakage accompanied by or preceded by urgency
- frequency = complaint of voiding too often by day
- nocturia = complaint of having to wake at night one or more times to void

What are the 2 major afferent nerve signals mediating the micturition reflex?

→ interstitial cells lie close to nerve fibers & likely play role in sensory transduction/regulation

- 1) myelinated A δ fibers } respond to **passive bladder distension & active detrusor contractions**
 - convey info about bladder filling
 - mediate N spinobulbospinal micturition reflex
- 2) unmyelinated C fibers } respond mainly to **chemical irritation** of urothelium & **thermal stimuli**
 - may be silent until pathologic stimuli present
 - may be involved in pathologic detrusor overactivity

→ **pathologically sensitized or abnormally numerous nerve endings may result in inappropriately high afferent activity, leading to detrusor overactivity and OAB**

What are the potential causes of detrusor overactivity?

- 1) **neurogenic** } detrusor overactivity arises from generalized, nerve-mediated excitation of muscle hypothesis
 - brain damage reduces supra-PMC inhibition
 - SC damage allows expression of primitive spinal bladder reflexes
 - synaptic neuroplasticity leads to reorganization of sacral activity w/ emergence of new C-fiber afferent mediated reflexes
 - sensitization of peripheral afferent terminals in bladder
- 2) **myogenic** } detrusor overactivity results from increased likelihood of spontaneous ctx's & enhanced propagation of activity hypothesis
 - patchy denervation leads to upregulation of action potentials
 - structural changes may lead to more spontaneous ctx's
- 3) **peripheral autonomy** } detrusor overactivity is due to enhanced coordination of modular ctx's through the myovesical plexus hypothesis
 - increased contractility of individual modules in bladder
 - enhanced communication between modules

PREVALENCE

How common is OAB?

- **10-15%**
 - “dry OAB” more common in M
 - “wet OAB” more common in F
 - more common with increasing age } especially wet OAB in women
- **most with OAB need Rx but most will not be cured**

CLINICAL ASSESSMENT

What is involved in the work-up of OAB?

- basic (initial) assessment gives a presumptive Dx and the basis for empirical Rx
- 1) history } characterize symptoms (urgency, frequency, nocturia, urgency incontinence)
 → quantification of OAB symptoms } frequency-volume chart, questionnaires
 } severity, bother, effect on QOL
 } voiding diary, fluid intake habits
 } PMHx, PSHx
 } desire for Rx
 - 2) physical } abdominal exam
 } neurologic exam
 } r/o PVR
 - 3) urine tests } urinalysis, urine C&S, +/- cytology
 - 4) initiate empiric Rx } lifestyle changes
 } bladder training
 } pelvic floor muscle training
 } meds (anti-muscarinics)
- UDS not recommended on initial evaluation } failure of empiric Rx or prior to invasive Rx

What are the normal bladder sensations?

- likely present even in OAB patients
- 1) first sensation of filling } ~150cc
 - 2) N desire to void } ~200cc
 - 3) strong desire to void } capacity

Table 61-1 -- Bladder Sensation Scale

- | | |
|---|---|
| 1 | No sensation of needing to pass urine but passed urine for "social reasons" (e.g., just before going out, unsure where next toilet is); no urgency. |
| 2 | Normal desire to pass urine; no urgency. |
| 3 | Urgency but urgency passed away before had to visit bathroom; went later with normal desire to pass urine. |
| 4 | Urgency but managed to get to bathroom still with urgency but did not leak urine. |
| 5 | Urgency and could not get to bathroom in time so leaked urine. |

Table 61-2 -- Cystometry Sensation Scale

- | | |
|---|--|
| 0 | No bladder sensation: "I don't feel anything." |
| 1 | First sensation of filling: "I'm beginning to feel my bladder." |
| 2 | First desire to pass urine: "I feel like I want to pass urine." |
| 3 | Urgency is graded.
Mild: "I think I can hold on."
Moderate: "I don't know if I can hold on."
Serious: "I have to go now or I will leak any moment." |
| 4 | Strong desire to pass urine: "I'm getting uncomfortable, I'd like to pass urine now." |

DISTINGUISHING OVERACTIVE BLADDER FROM PAINFUL BLADDER SYNDROME

What is painful bladder syndrome?

- complaint of suprapubic pain related to bladder filling, accompanied by other symptoms (such as frequency, nocturia)
- pain builds up slowly from discomfort to pain
- need to r/o other causes } eg UTI, TCC, etc

How can you differentiate OAB from PBS?

	OAB	PBS
Symptoms	<ul style="list-style-type: none">- urgency is main symptom- sudden onset of desire to void and pain- symptoms felt lower down in pelvis/genitalia	<ul style="list-style-type: none">- pain is main symptom- gradual onset of pain and need to void- suprapubic pain
continence	<ul style="list-style-type: none">- involuntary leak (except OAB dry)	<ul style="list-style-type: none">- can hold urine voluntarily, but at cost of more pain- voluntary leakage due to pain
voided volume	<ul style="list-style-type: none">- variable	<ul style="list-style-type: none">- fairly consistent volumes throughout day

URODYNAMIC CONFIRMATION OF DETRUSOR OVERACTIVITY

What are the arguments against UDS on initial evaluation?

- 1) OAB is common and would overwhelm UDS facilities
- 2) UDS is relatively invasive & expensive and may not demonstrate detrusor overactivity
- 3) conservative Rx (lifestyle changes & anti-muscarinics) are safe and relatively cheap

How often does UDS demonstrate detrusor overactivity?

- good correlation between “OAB wet” and detrusor overactivity
- poor correlation with “OAB dry”
- poor correlation if coexisting stress incontinence (mixed picture)
- can also see asymptomatic detrusor overactivity
- more physiologic and more likely to demonstrate detrusor overactivity if filling occurs with patient in sitting or standing position
- **supine position can mask presence of overactivity**

What are the 2 main patterns of detrusor overactivity seen on UDS?

- 1) **phasic** } characteristic phasic waveform and may or may not lead to incontinence
 - increasing amplitude as bladder volume increases
 - more common in idiopathic detrusor overactivity
 - 2) **terminal** } single involuntary contraction occurring at capacity, which can't be suppressed and causes incontinence and leads to bladder emptying
 - more common in neurogenic detrusor overactivity
- **there is no proscribed minimum value for a “significant” involuntary detrusor ctx**

MANAGEMENT

What are the management options for OAB?

- 1) conservative Rx
 - behaviour therapy (“BEHaVe”)
 - Bladder training } timed/scheduled voiding, urge inhibition techniques, etc
 - Education } anatomy & function
 - Habits } decrease caffeine intake, fluid restriction prn, decrease carbonated drinks, wt loss, improved bowel habits
 - Voiding diary
 - PFMT
 - biofeedback
 - external devices
- 2) meds
 - oral
 - anti-muscarinics
 - membrane channels meds
 - TCAs
 - α -blockers
 - β -agonists
 - PG synthesis inhibitors
 - DDAVP
 - intravesical
 - anti-muscarinics
 - vanilloids (resiniferatoxin, capsaicin)
 - botox
- 3) surgery
 - neuromodulation
 - detrusor myectomy/myotomy
 - augmentation cystoplasty
- 4) treatment of intractable/refractory OAB
 - catheters (urethral or suprapubic)
 - appliances
 - urethral closure + diversion

List conditions that are considered “COMPLICATED” incontinence.

- recurrent incontinence
- incontinence associated with:
 - pain
 - hematuria
 - recurrent UTIs
 - voiding symptoms
 - pelvic RADs
 - radical pelvic surgery
 - suspected fistula

AUA Update #15 - 2008

What are the 4 steps required for toxin induced paralysis?

- 1) binding of toxin heavy chain to specific nerve terminal receptor
- 2) internalization of toxin within nerve terminal
- 3) translocation of light chain into cytosol
- 4) inhibition of NT release

List the potential GU applications of Botulinum toxin.

- neurogenic detrusor overactivity (100-300 units)
- idiopathic detrusor overactivity (100-300 units)
- IC/Painful Bladder syndrome
- Chronic Pelvic Pain Syndrome (CPPS) (100-200 units) → transvaginal or perineal
- BPH (100-200 units) → transrectal or perineal
- DESD (50-200 units) → transurethral or perineal

How does Botulinum toxin work for OAB?

- decreases cholinergic nerve-induced bladder activity
- inhibition of sensory input from urothelium
- inhibition of bladder nerve growth factor release

How does Botulinum toxin work for BPH?

- chemical denervation of prostate (by blocking Ach release) can induce glandular apoptosis/atrophy
- blockade of other NTs (eg NE) can result in relaxation of normal prostatic tone

List the potential complications related to GU injections of Botulinum toxin

- muscle weakness
- dry mouth
- retention needing CIC
- new SUI
- exacerbation of pre-existing incontinence

List contraindications to Botulinum toxin injections.

- “BLAME Poison”
- **B**reastfeeding
- **L**ou Gherig disease (ALS)
- **A**minoglycoside use
- **M**yasthenia gravis
- **E**aton-Lambert syndrome
- **P**regnancy

Chapter #62 – Pharmacologic Management of Storage & Emptying Failure

PHARMACOLOGIC THERAPY TO FACILITATE BLADDER FILLING AND URINE STORAGE

OAB and Detrusor overactivity

What are the non-surgical options for incontinence caused by detrusor overactivity?

→ URGE INCONTINENCE

- 1) treat all remediable causes } eg UTI, urethral obstruction, bladder stone, FBs, bladder Ca, BPH, herniated lumbar disk, prolapse,
 - TURP improves OAB symptoms in 2/3 of men w/ BPH
 - urethrolisis improves OAB symptoms in ~70% of women w/ BOO due to anti-incontinence Sx
- 2) behaviour therapy (BEHaVe) } Bladder training (timed voiding, urge inhibition techniques, etc), Education, Habits (fluid intake, caffeine, wt loss), Voiding diary
- 3) pelvic floor muscle training } Kegels, biofeedback, vaginal cones, electrical stimulation
- 4) oral meds } anti-muscarinics
 - most have partial efficacy (increased volume to 1st involuntary contraction, decrease in amplitude, increase in capacity)
 - M3 is most important receptor but M2 is 3-4x more common in bladder
 - } TCAs
 - imipramine } direct relaxant effect on detrusor, sympathomimetic effect on BN & central effects
 - } muscolotropic relaxants eg flavoxate
- 5) intravesical meds } oxybutynin
 - } capsaicin (block vanilloid receptors – C fiber afferents)
 - initial excitatory effect followed by prolonged desensitization
 - use limited by pain and hematuria post instillation
 - } resiniferatoxin (block vanilloid receptors – C fiber afferents)
 - 1000x more potent than capsaicin but no initial excitatory effect
 - } botox A (100-300 units)
 - inhibits acetylcholine release at presynaptic junction
- 6) neuromodulation } induction of somatic afferent inhibition of sensory processing in SC
 - **S3 dorsal root**
 - } temporary lead trial and if +ve response (>50% improvement) then permanent neurostimulator implanted
 - mainly for non-neurogenics
 - 2nd line Rx

What muscarinic cholinergic receptors are found in the bladder?

- **major portion of neurohumoral stimulus for bladder ctx's is acetylcholine-induced stimulation of postganglionic parasympathetic muscarinic cholinergic receptors**
- **also evidence of clinically relevant non-adrenergic, non-cholinergic (NANC) receptors**
- predominantly M2 and M3 receptors in bladder } evidence of all five receptors (M1-M5)
 - **M2 receptors 3x more common** than M3 receptors in bladder
 - **M3 receptors are most important** for contractions
 - M2 receptors play small role in N bladder ctx's } larger role in disease states (neurogenic)
- receptors found on detrusor muscle cells as well as other bladder structures (urothelium, nerves, etc)

What is the signaling mechanism for M3 receptors?

- M3 receptor coupled to G protein } activates phosphoinositide hydrolysis
- mobilizes intracellular Ca via nifedipine-sensitive L-type Ca²⁺ channels
- also results in activation of Rho kinase pathway

What different meds have been used for detrusor overactivity (CHART)?

→ **grade A recommendations**

- antimuscarinics } tolterodine
- } trospium
- } solifenacin
- } darifenacin
- mixed action drugs } oxybutynin
- } propiverine
- other } desmopressin

→ grade B recommendations

- antimuscarinics } propantheline
- other } botulinum toxin

→ grade C recommendations

- antimuscarinics } atropine
- mixed action drug } dicyclomine
- antidepressants } imipramine
- α -blockers } alfuzosin
- } doxazosin
- } prazosin
- } terazosin
- } tamsulosin
- β -blockers } terbutaline
- } salbutamol
- COX inhibitors } indomethacin
- } flurbiprofen
- other } capsaicin, resiniferatoxin,
 baclofen

How do anti-muscarinics work in detrusor overactivity?

→ block muscarinic receptors on detrusor muscle that are stimulated by acetylcholine, released from parasympathetic nerves

- 1) ↓'s urgency (increases volume to 1st involuntary contraction)
- 2) ↑'s bladder capacity
- 3) ↓'s ability of bladder to contract } competitive antagonist so can be overcome w/ massive release of acetylcholine during N micturition

→ does not increase “warning time” and does not alter compliance

→ most anti-muscarinics are metabolized by CYP-450 enzyme system in liver

What are the different types of anti-muscarinics?

→ tertiary amines

- higher lipophilicity, less molecular charge, smaller size } passes through BBB
- tolterodine, oxybutynin (mixed), darifenacin, solifenacin, atropine
- hepatic clearance

→ quaternary amines

- low lipophilicity, higher charge, larger size } DO NOT PASS THROUGH BBB
- **trospium, propantheline**
- renal clearance

What are the potential side effects of anti-muscarinics? (AUA Update #16 – 2008)

→ inhibition of salivary secretions (M3 in parotid)

} dry mouth

→ blockade of sphincter muscle of iris & ciliary muscle of lens (M3 in iris)

- } blurred vision

} photophobia

→ inhibition of bowel motility (M2 and M3 in colonic smooth muscle)

} constipation

} dyspepsia

$$\} \quad N/V$$

→ cardiovascular effects (post-junctional M2 in heart)

- } tachycardia

→ cognitive dysfunction (M1 & M2 in brain)

} confusion

} hallucinations

→ local bladder smooth muscle

- } urinary retention

List the grade A recommended anti-muscarinics used for OAB-detrusor overactivity

→ based on level 1 evidence (RCTs)

- tolterodine } Detrol 2mg BID, Detrol LA 4mg OD
 - **1st line therapy**
 - } **NON-SELECTIVE** for any muscarinic receptors
 - } T_{1/2} = 2-3hrs
 - } metabolized in liver by CYP-450
 - } dry mouth is most common side effect, **QT prolongation risk**
- trospium } Trosec/Sanctura 20mg BID
 - **need to take twice daily**
 - } **NON-SELECTIVE quaternary amine** with low bioavailability (<10%)
 - } does NOT cross BBB
 - **theoretically less cognitive impairment**
 - } T_{1/2} = 20hrs
 - } mainly renal elimination
 - **can't use in renal failure**
 - } dry mouth is most common side effect, **constipation may be more common**
- solifenacin } Vesicare 5mg or 10mg OD
 - **can dose escalate**
 - } **relative M₃ selective** receptor blocker
 - } tertiary amine with good bioavailability (90%)
 - } T_{1/2} = ~2days
 - } hepatic metabolism (CYP-450)
 - } dry mouth is most common side effect
- darifenacin } Enablex 7.5mg or 15mg OD
 - **can dose escalate**
 - } **M₃ SELECTIVE** receptor blocker
 - **less cognitive impairment (M₁ in brain)**
 - } T_{1/2} = 18hrs
 - } hepatic metabolism (CYP-450)
 - } dry mouth is most common side effect; **constipation more common**

What other anti-muscarinics are used for OAB-detrusor overactivity?

→ grade B recommended

- propantheline } quaternary amine with low bioavailability (5-10%)
- } T_{1/2} = 1-2hrs

→ grade C recommended

- atropine (hyoscyamine) } significant systemic side effects
- } intravesical atropine better

What are the contraindications to anti-muscarinics? }}} "GO CHUG MILK"

→ absolute

- 1) **G**laucoma (narrow angle)
- 2) **O**bstructed bowel

→ relative

- 3) **C**ardiac disease + HTN
- 4) **H**yperT₄
- 5) **U**rinary obstruction (BOO)
- 6) **G**ERD
- 7) **M**yasthenia gravis
- 8) **I**mpaired cognition
- 9) **L**iver failure
- 10) **K**idney failure

What is the role of OXYBUTYNIN in OAB-detrusor overactivity?

→ **grade A recommendation } drug with “mixed” actions**

- relative M1 and M3 selectivity
- Ditropan 5mg BID/TID, Ditropan XL 5mg or 10mg OD, Oxytrol patch 3.9mg/day
 - **1st line therapy**
 - dry mouth most common S/E
 - less common w/ Ditropan XL & Oxytrol patch (no first pass effect)
- **mainly anti-muscarinic effect** but also has other affects
 - **direct smooth muscle relaxant effect + local anesthetic action**
- **especially good for neurogenic voiding dysfunction**
- $T_{1/2} = 2\text{hrs}$
- metabolized in liver CYP-450

What other drugs with “mixed” action can be used for OAB-detrusor overactivity?

→ grade A recommended

- propiverine } anti-muscarinic effect + CCB effect
 - } $T_{1/2} = 12\text{hrs}$
 - } hepatic metabolism
 - } fewer side effects than oxybutynin

→ grade C recommended

- dicyclomine } anti-muscarinic effect + direct relaxant effect on detrusor (limited data)

→ grade D recommended

- flavoxate } CCB effect + inhibits phosphodiesterase + local anesthetic effect
 - } very few side effects but limited efficacy

What is the role of α -blockers and β -agonists in OAB-detrusor overactivity?

- limited role for α -blockers } more common in proximal urethral than bladder body
- β_2 agonists shown to be ineffective
- β_3 agonists being studied } most common in bladder body

What is the role of CCBs and K⁺ channel openers in OAB-detrusor overactivity?

- blocking intracellular Ca influx would decrease detrusor overactivity
 - **no evidence for systemic CCBs**
- influx of K⁺ would hyperpolarize smooth muscle cells and decrease Ca²⁺ influx, leading to inhibition of contraction
 - **no evidence for systemic K⁺ channel openers**

What is the role of antidepressants in OAB-detrusor overactivity?

→ grade C recommendation

→ **TCAs have 4 main effects**

- 1) **anti-muscarinic effects (central & peripheral)**
- 2) **selective serotonin & NE reuptake inhibitor**
- 3) **sedative effective**
- 4) **direct smooth muscle relaxant (not in Campbell's)**

→ eg imipramine, duloxetine, doxepin } **contraindicated in patients on MAOIs**

→ suppresses bladder overactivity

→ closure of BN and proximal urethra

What are the potential side effects of TCAs?

- dry mouth, blurred vision
- HTN, orthostatic hypoTN, arrhythmias (prolongs QT interval)
- numbness, tingling, parkinsonism
- skin rash, itching, sweating
- BM suppression (agranulocytosis)
- N/V, diarrhea, jaundice
- ED, gynecomastia
- suicide risk with duloxetine

What is the role of botulinum toxin in OAB-detrusor overactivity?

→ **grade B recommendation**

- botox type A and B in clinical use } 7 total subtypes (A, B, C1, D, E, F, G)
- blocks release of acetylcholine + other NTs from presynaptic NMJ nerve endings
- reversible process } axons regenerate in 3-6 months
- can't cross BBB } no CNS effects
- no tachyphylaxis
- **increased capacity, decreased max Pdet**

How does Botulinum toxin work? (AUA Update #15 - 2008)

→ single chain polypeptide with molecular weight of 150 kDa

→ **prevents release of acetylcholine from pre-synaptic nerve terminal in NMJ**

- toxin binds to & cleaves cytosolic translocation protein (SNARE/SNAP-25), preventing vesicle with NTs from fusing with plasma membrane
- heavy chain allows entrance in nerve terminal, light chain cleaves proteins
- prevention of the release of NTs from the pre-synaptic nerve terminal results in paralytic effect

List potential GU applications of Botulinum toxin. (AUA Update #15 - 2008)

- neurogenic detrusor overactivity (100-300 units)
- idiopathic detrusor overactivity (100-300 units)
- IC/Painful Bladder syndrome
- Chronic Pelvic Pain Syndrome (CPPS) (100-200 units → transvaginal or perineal)
- BPH/tight BN (100-200 units → transrectal or perineal)
- DESD (50-200 units → transurethral or perineal)

List contraindications to Botulinum toxin injections. (AUA Update #15 - 2008)

→ **“BLAME Poison”**

- **B**reastfeeding
- **L**ou Gherig disease (ALS)
- **A**minoglycoside use (concomitant)
- **M**yasthenia gravis
- **E**aton-Lambert syndrome
- **P**regnancy

What is the role of intravesical vanilloids in OAB-detrusor overactivity?

→ grade C recommendation

- capsaicin & resiniferatoxin (RTX) act on afferent C fibers by initially exciting nerves then eventually causing desensitization
- RTX 1000x more potent at desensitization & only 300x more potent for excitation

What medications have been used for overactivity in augmented or intestinal neobladder?

→ local meds better than systemic meds

- oxybutynin
- CCBs
- NO donors
- opioid agonists
- K⁺ channel openers

SUI

List non-surgical options for incontinence caused by sphincteric dysfunction?

→ STRESS INCONTINENCE

- 1) behaviour modification } decreased fluid intake, dietary & lifestyle changes, timed voiding
- 2) pelvic floor muscle training } Kegels, biofeedback, vaginal cones, electrical stimulation
 - RCT shows PFMT is better than no treatment for SUI
 - no added benefit of biofeedback + PFMT
- 3) oral meds } α -agonists (increases urethral muscle tone eg ephedrine, PPA, midodrine)
 - only weak evidence showing they are better than placebo
 - } SNRIs (eg duloxetine)
 - } TCAs (eg imipramine)
- 4) pessaries } for prolapse related SUI
- 5) topical meds } estrogen → LIMITED TO NO ROLE FOR SUI

What are the targets of medical Rx for SUI?

- urethral tone mediated by α -adrenergics in urethral smooth muscle } NE
- EUS tone mediated through Onuf's nucleus } serotonin and NE

What medications have been used in the treatment of SUI (CHART)?

- grade A recommendation
 - duloxetine } selective NE & serotonin reuptake inhibitor
 - 40mg BID or 80mg OD (not approved by FDA, ok in Europe)
 - hepatic metabolism with $T_{1/2} = 12\text{hrs}$
- grade C recommendation
 - midodrine } selective α_1 -agonist
 - limited efficacy
- grade D recommendation
 - imipramine } selective NE & serotonin reuptake inhibitor (works at level of urethra & Onuf's)
 - 25mg TID or 75mg OD
 - side effects can be serious
 - methoxamine } selective α_1 -agonist
 - limited by side effects (H/A, cold extremities, piloerection)
 - α -agonists } ephedrine
 - 25-50mg QID
 - little benefit in severe SUI
 - central stimulation issues } HTN, stroke, seizures, etc
 - } norephedrine (PPA)
 - 25-75mg BID
 - cure in 0-15% & improvement in 20-60%
 - less central stimulation than ephedrine
 - high risk of hemorrhagic stroke (16x) } taken off market
 - estrogen } limited role for SUI
 - may have role as part of combination therapy

What is the role of desmopressin for treatment of nocturia?

- aka "DDAVP"
- synthetic vasopressin w/ pronounced anti-diuretic effect } for nocturnal enuresis & nocturia
- intranasal (20-40µg) and oral formulations } more bioavailable in intranasal form

What are the potential side effects of DDAVP?

- hyponatremia
- water retention
- H/A
- nausea
- mild abdominal cramps

List contraindications to DDAVP therapy.

- CHF
- HTN
- liver disease
- Crohn's disease
- primary polydipsia

PHARAMACOLOGIC THERAPY TO FACILITATE BLADDER EMPTYING

Increasing Intravesical Pressure and Bladder Contractility

What medications have been used to increase bladder contractility?

- 1) bethanecol (5-10mg SC) } cholinergic agonist
 - } selective in vitro action on bladder and guts
 - causes detrusor contraction & increases GI motility
 - no nicotinic action
 - } resistant to cholinesterase
 - } may increase urethral resistance
 - better if used with α -blockers
 - } SC dosing requires intact micturition reflex
 - incomplete LMN lesions most reasonable for trial
 - “denervated” bladder needs high PO dose
 - } limited efficacy with ++ side effects
- 2) metoclopramide } dopamine receptor antagonist with cholinergic properties
 - } increases LES tone + antiemetic effects + blocks inhibitory effect of dopamine on bowel contractility
 - may also increase detrusor contractility
- 3) cisapride } synthetic benzamide that enhances release of acetylcholine in Auerbach’s plexus
 - may decrease cystometric capacity
 - prolongs QT interval (dangerous arrhythmias) } OFF MARKET
- 4) PGs } plays a role in maintaining bladder tone and bladder contractile activity
 - limited efficacy with no long term results
- 5) opioid receptor blockers } may stimulate reflex bladder activity by blocking inhibitory effects of opioids on micturition reflex
 - limited role

Why can’t acetylcholine be used to increase bladder contractility?

- activation of parasympathetic postganglionic muscarinic cholinergic receptors is key to bladder ctx
- acts at both muscarinic AND nicotinic receptors
- rapidly hydrolyzed by acetylcholinesterase and butyrylcholinesterase

What are the contraindications to bethanecol? What are potential side effects of bethanecol?

- | | |
|--------------------------------|--------------------------------|
| → similar for all cholinergics | → similar for all cholinergics |
| - bronchial asthma | - flushing |
| - PUD | - N/V |
| - bowel obstruction | - diarrhea |
| - enteritis | - GI cramps |
| - recent GI surgery | - bronchospasm |
| - cardiac arrhythmias | - H/A |
| - hyperT4 | - salivation |
| - BOO | - sweating |
| - recent bladder surgery | - blurry vision |
| - pregnancy | - can get circulatory arrest |

What are the potential roles of PGs in the bladder?

- 1) neuromodulators of efferent and afferent neurotransmission
- 2) sensitization of sensory nerves
- 3) activation of sensory nerves
- 4) potentiation of acetylcholine release from cholinergic nerve endings

Which PGs are found in the human bladder?

- PGE₂ > PGE₁ > PGF_{2α} > thromboxane A₂
- PGE₂ is most common } causes net decrease in urethral smooth muscle tone
- PGF_{2α} } causes net increase in urethral smooth muscle tone

What are the potential side effects of PGs?

- N/V
- diarrhea
- fever
- HTN or hypoTN

Decreasing Outlet Resistance

What medications have been used to decrease outlet resistance (CHART)? } } } “AID 4 Bladder”

- 1) **Alpha-blockers** } relaxes smooth muscle in lower GU tract and prostate
 } ideal for smooth sphincter or BN dyssynergia/dysfunction
 } relaxes BN & proximal urethra + decreases striated sphincter tone
 → may even decrease bladder contractility
- 2) **NO donors (Isosorbide dinitrate 10mg)** } induction of urethral smooth muscle relaxation
 → particularly good for DSD in SCI patients
- 3) **Dantrolene (25mg OD - 100mg QID)** } anti-spasmodic that inhibits excitation-induced release of Ca
 → reduces reflex ctx's more than voluntary ctx's
 } significant side effects at high doses needed for efficacy
 → limited mainly by generalized weakness
- 4) **Benzodiazepines** } muscle relaxant + anti-anxiety + sedative + anticonvulsant
 → effects may be more anxiolytic-related than muscle relaxant
 → doesn't work well for DESD } better for dysfunctional voiders
 } potentiates central inhibitory effects of GABA via GABA-A receptors
- 5) **Baclofen (5-25mg BID/QID)** } anti-spasmodic that depresses neuronal excitation by
 activating inhibitory GABA-B receptors
 } oral formulation relatively ineffective
 → intrathecal dosing more effective
 } side effects common at high PO doses needed for efficacy
- 6) **Botulinum toxin** } inhibits release of acetylcholine and other NTs at NMJ
 → prevents spasm and involuntary contractions, but incompletely
 blocks voluntary control
 → use for DSD
 } injection into EUS either transurethrally or transperineally
 } minimal side effects
- 7) **others** } **α-Bungaratoxin** (iv)
 → from Formosan snake venom
 → selectively blocks nicotinic receptors in EUS
 → trials in rats only

What type of α-adrenergic receptors are found in the lower GU tract?

- α₂ receptors are more common
- α₁ receptors are more important in mediating smooth muscle contractions in lower GU tract & prostate
 → there are 3 subtypes of α₁ receptors } α_{1A}, α_{1B}, α_{1D}
 } mainly α_{1A} mediated contractions (tamsulosin)

What are the different α -blockers that have been used to decrease outlet resistance?

- 1) phenoxybenzamine (10mg OD) } α_1 and α_2 blocker (irreversible)
 } side effects seen in ~30%
- 2) prazosin (2-5mg BID) } selective α_1 blocker
 (Minipress) } short half life
 } needs to be titrated
 } can have first-dose phenomenon (side effects)
- 3) terazosin & doxazosin & alfuzosin } selective α_1 blocker
 (Hytrin) (Cardura) (Xatral) } longer half life (OD dosing)
 } needs to be titrated
 } less side effects
 → postural hypoTN, weakness, dizziness, asthenia
 (worse with doxazosin)
 → alfuzosin has similar S/E profile as α_1A blocker
- 4) tamsulosin } α_{1A} blocker
 (Flomax) } longer half life (OD dosing)
 } no need for dose titration
 } similar side effects
 → retrograde ejaculation & rhinitis more common

What are the contraindications to α -blocker therapy?

- known hypersensitivity to α -blocker
- upcoming cataract surgery (floppy iris syndrome)
- previous life-threatening sulfa allergy
- postural hypoTN
- hx of priapism (relative)
- pregnancy (relative)

What are the common S/Es of α -blocker therapy?

- fatigue/asthenia
- runny nose/rhinitis
- dizziness } not related to CV effect of meds but due to CNS effect (most with prazosin, then doxazosin)
- syncope/hypoTN
- headache
- GI upset
- retrograde ejaculation } incidence different with different meds (eg flomax > xatral)
- priapism

What are the potential side effects of phenoxybenzamine?

- orthostatic hypoTN
- reflex tachycardia
- nasal congestion
- diarrhea
- miosis
- sedation
- N/V
- carcinogenic } GI, lung, sarcomas

What are the potential side effects of prazosin?

- faintness
- dizziness
- palpitations
- syncope

Chapter #63 – Conservative Mgt of Urinary Incontinence

GENERAL CONSIDERATIONS

How common is urinary incontinence in WOMEN?

- 5-20% prevalence
- increasing prevalence with age
- prevalence of severe incontinence is 5-10%
- overall, **SUI is most common (~50%)**, then mixed (~30%) and urge (~20%)
- proportion of types of incontinence varies with age
 - **SUI is most common in young & middle-aged women**
 - **mixed incontinence is most common in older women**

How common is urinary incontinence in MEN?

- 3-10% prevalence
 - about 1/2 as prevalent as women
- increasing prevalence with age
 - rises more steadily than women
- overall, **urge incontinence is most common (40-80%)**, then mixed (10-30%) and stress (<10%)
 - SUI is the least common type unless associated with RP, neurologic injury, or trauma

List some of the morbidities associated with urinary incontinence.

- falls
- fractures
- UTIs
- skin breakdown/dermatitis
- pressure ulcers
- admission to NH
- psychological effects } poor self-esteem, depression, etc
- poor sex life

List arguments in favor of trial of conservative therapy for incontinence before surgery.

- although important to r/o serious underlying or associated conditions, invasive testing is **RARELY REQUIRED** before initiating treatment with conservative measures
- 1) progression NOT inevitable } moderate delay in surgical Rx doesn't make future Rx more difficult
- 2) conservative Rx's are safe, effective, and well tolerated
- 3) conservative Rx is preferred by many patients

THE TOOLS OF CONSERVATIVE THERAPY & CONCEPT OF 'THERAPEUTIC PACKAGE'

What are the non-surgical “conservative” options used for urinary incontinence?

- 1) behaviour therapy (“BEHaVe”)
 - Bladder training } timed/scheduled voiding, urge inhibition techniques, etc
 - Education } anatomy & function
 - Habits } decrease caffeine intake, fluid restriction prn, decrease carbonated drinks, wt loss, improved bowel habits
 - Voiding diary
- 2) Pelvic floor muscle training (Kegels, etc)
- 3) biofeedback
 - direct palpation
 - vaginal cones
 - office machines
- 4) peripheral electrical & magnetic stimulation
 - high-frequency stimulation of vagina or anal sphincter for SUI
 - low-frequency stimulation of inhibitory nerves to bladder for Urgency incontinence (eg posterior tibial nerve)
 - Grade C recommendation for magnetic stimulation (external device used in clinic setting only)
- 5) external devices
 - supportive } pessary ring
 - occlusive } meatal occlusive devices, urethral inserts

Which patient population has the best long term results with conservative behavioural Rx (CHART)?

	Cure/Improve	Relapse
→ normal CMG	94%	6%
→ ↓'d compliance	90%	42%
→ idiopathic instability	90%	44%
→ neurogenic	50%	100%

List conservative measures that have NO EVIDENCE in improving urinary incontinence.

- smoking cessation
- stress reduction
- wearing non-restrictive clothing
- increasing sexual activity
- use of cotton underwear

How well do conservative measures work for urinary incontinence?

- bladder retraining } 85% initial response, 50% 3yr response
- PFMT } 40-50% can avoid surgery for SUI
- **Level 1 evidence in support of behaviour Rx + PFMT as 1st line Rx for incontinence, regardless of type of incontinence (SUI, UII, MUI)**

PELVIC FLOOR REHABILITATION

What is the role of PFMT?

- program of repeated voluntary pelvic floor muscle contractions taught by a health care professional
- used for both prevention & treatment of incontinence
- **Grade A evidence to support PFMT as 1st line therapy for incontinence, regardless of type**
- Grade B evidence to support PFMT in an attempt to prevent incontinence in women after delivery of a large infant or instrumental delivery
- **limited role for PFMT in post-RP incontinence**
 - earlier return of continence
 - better results in those with mild incontinence
 - NO long-term benefit, regardless of whether done to prevent or to treat for post-RP SUI
- **no benefit of adding Biofeedback to PFMT alone**
- Grade B evidence to suggest PFMT has worse outcomes than surgery
- Grade B evidence that PFMT has similar outcomes to behaviour therapy & vaginal cones
- Grade B evidence to suggest that PFMT is better than oxybutynin (for UUI) & electrical stimulation

DEVICES

What are the advantages & disadvantages of vagina support devices?

→ ADVANTAGES

- potentially wide applicability
- no specific testing required
- can be used on PRN basis
- mild side effects (occasional vaginitis)
- some devices used for both POP & SUI

→ DISADVANTAGES

- does not correct ISD
- not a definitive solution/cure

List 3 specific roles of a vaginal pessary for LUTS.

- 1) identification of “occult” SUI in a patient with cystocele
- 2) identification/treatment of symptomatic prolapse causing OAB symptoms
- 3) identification/treatment of symptomatic cystocele causing LUTS and/or retention

PRACTICAL APPROACH TO TREATMENT

List the 4 most important details used to guide therapy.

- 1) type of urinary incontinence
 - behavioural therapy + PFMT recommended as 1st line REGARDLESS of type of incontinence
- 2) baseline voiding diary
 - largest voided volume on diary correlates well with cystometric capacity defined on UDS
- 3) assessment of anatomy & function } pelvic floor muscle strength
 - a) those with minimal or no ability to isolate & contract levators
 - Rx → biofeedback training +/- passive stimulation
 - b) those that can isolate levators but have poor muscle strength
 - Rx → PFMT
 - c) those with good pelvic floor muscle strength & isolation
 - Rx → PFMT (if mild incontinence) or medical or surgical Rx (if severe)
- 4) patient goals } “EGGS”
 - expectations
 - goal setting
 - goal achievement
 - satisfaction

What are the main options for SUI?

- behaviour therapy
- PFMT
- meds } oral (α -agonists, TCAs, SNRIs, etc)
- external devices
- surgical treatment } urethral bulking agents
- } PVS, midurethral slings
- } suspensions (retropubic, needle)
- } AUS
- } diversion (only for refractory excessive SUI)

What are the main options for OAB and Urgency incontinence?

- behaviour therapy
- PFMT
- meds } oral (anti-muscarinics, TCAs, smooth muscle relaxants) & intravesical (Botox-A)
- neuromodulation
- surgical treatment } augments
- } denervation
- } diversion

Which patients should be offered pharmacologic treatment early on?

- low maximal voided volume on diary
- underlying neurologic disease
- patients uninterested or unable to participate in behaviour therapy or PFMT

Which patients should be offered surgical treatment early on?

- associated pelvic organ prolapse (beyond hymenal ring)
- highly motivated to be completely dry
- those with high levels of physical stress due to lifestyle or occupation (eg sports athlete)
- severe SUI
- those with good pelvic floor muscle strength & isolation

List the advantages & disadvantages of intravesical Botox-A cf neuromodulation in the Rx of OAB/UII.

→ advantages

- lower initial cost
- less invasive
- no permanent implant

→ disadvantages

- need for repeat injections
- no long-term studies

AUA Update #15 - 2008

List the potential GU applications of Botulinum toxin.

- neurogenic detrusor overactivity (100-300 units)
- idiopathic detrusor overactivity (100-300 units)
- IC/Painful Bladder syndrome
- Chronic Pelvic Pain Syndrome (CPPS) (100-200 units → transvaginal or perineal)
- BPH (100-200 units → transrectal or perineal)
- DESD (50-200 units → transurethral or perineal)

How does Botulinum toxin work for OAB?

- decreases cholinergic nerve-induced bladder activity
- inhibition of sensory input from urothelium
- inhibition of bladder nerve growth factor release

List the potential complications related to GU injections of Botulinum toxin

- muscle weakness
- dry mouth
- retention needing CIC
- new SUI
- exacerbation of pre-existing incontinence

List contraindications to Botulinum toxin injections.

- BLAME Poison
- **B**reastfeeding
- **L**ou Gherig disease (ALS)
- **A**minoglycoside use
- **M**yasthenia gravis
- **E**aton-Lambert syndrome
- **P**regnancy

Chapter #65 – Retropubic Suspension Surgery for Incontinence in Women

THERAPEUTIC OPTIONS

What are the management options for incontinence caused by sphincteric dysfunction?

→ STRESS INCONTINENCE

- 1) Behaviour Rx } Bladder training (timed voiding, etc), Education, Habit changes (fluid intake, caffeine, bowel habits, etc), Voiding diary
- 2) Pelvic floor muscle training } Kegels, biofeedback, vaginal cones, electrical stimulation
→ RCT shows PFMT is better than no treatment for SUI
→ no added benefit of biofeedback-PFMT
- 3) oral meds } α -agonists (increase urethral muscle tone eg ephedrine, PPA, midodrine)
→ only weak evidence showing they are better than placebo
} SNRIs (eg duloxetine)
} TCAs (eg imipramine)
- 4) pessaries } for prolapse related SUI
- 5) topical meds } estrogen → LIMITED TO NO ROLE FOR SUI
- 6) urethral bulking agents } collagen, PTFE, hyaluronic acid/dextranomer (Zuidex/Deflux), polydimethylsiloxane elastomer (Macroplastique)
→ short-duration of effect
- 7) surgery } PVS & midurethral slings
} urethral culposuspension (open vs laparoscopic)
} needle suspensions
} AUS
} vaginal anterior repair (anterior colporrhaphy)
- 8) diversion } only considered for refractory cases with severe sphincteric damage

What are the surgical options for management of SUI (CHART)?

- 1) periurethral injections
- 2) suspensions } open retropubic colposuspension
} laparoscopic retropubic colposuspension
} needle suspension
- 3) suburethral slings } PVS
} midurethral slings
- 4) AUS
- 5) vaginal anterior repair (anterior colporrhaphy)
- 6) diversion

→ anti-incontinence surgery does not work to restore the same mechanism of continence that was present before the onset of SUI, but it works by a compensatory approach

→ surgical outcomes are influenced by several variables

- age
- post-op activity
- prior Sx
- ISD
- concomitant OAB
- medical comorbidities
- duration of symptoms
- obesity

What are some pertinent conclusions of the current existing literature on suspensions for SUI?

- age may not be a contraindication to colposuspension } some suggest worse outcomes w/ age
- medical comorbidity may have an impact on surgical outcomes
- psychological factors may also have an impact on subjective and objective outcomes
- obesity is controversial and may or may not increase failure rates
- surgery for recurrent SUI has lower success rates
- severity and duration of pre-op symptoms may predict outcomes
- outcomes far worse for mixed incontinence cf pure SUI
- there is no evidence to suggest that ISD affects outcomes or the type of surgical treatment

CHOICE OF SURGICAL TECHNIQUE

What are the 2 main factors involved in SUI?

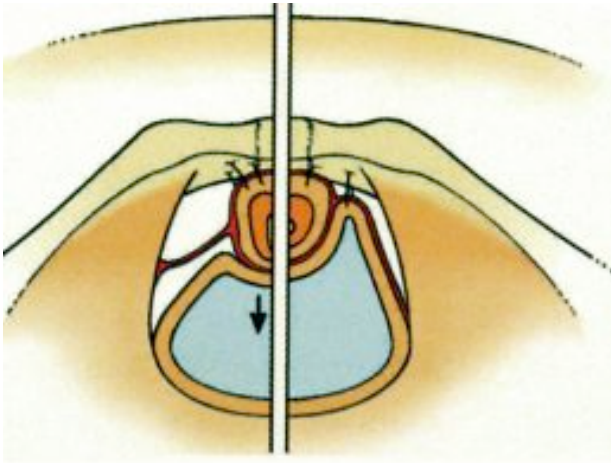
- 1) urethral hypermobility (weakening or loss of supporting elements) } not present in all cases
- 2) ISD (intrinsic deficiency of urethral itself) } present to some degree in all cases of SUI

What is the goal of retropubic procedures for SUI?

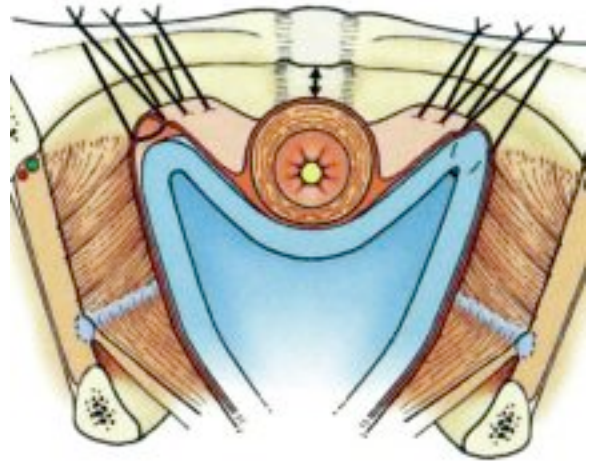
- restores BN and proximal urethral to a fixed, retropubic position
→ **good for SUI where urethral hypermobility is main cause**
- may facilitate function of a marginally compromised intrinsic sphincter mechanism
→ **SUI will persist if severe ISD exists**

What are the different types of retropubic colposuspensions?

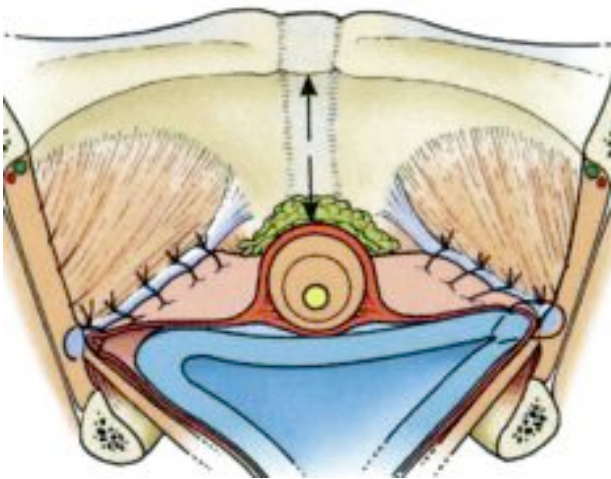
- 1) open retropubic colposuspension
 - lifting tissues near BN & proximal urethra into area behind the anterior pubic bones
 - 4 variations } **Marshall-Marchetti-Krantz**
 - suspension of BN toward periosteum of symphysis pubis
 - suture dependent in long-term
 - } **Burch**
 - elevation of anterior vaginal wall + paravesical tissues toward iliopectineal line of pelvic sidewall
 - V-shaped suspension increases obstructive problems
 - suture dependent in long-term
 - } **paravaginal**
 - closure of presumed fascial weakness laterally at site of attachment of pelvic fascia to internal obturator fascia
 - horizontal suspension makes obstructive problems less common
 - } **vagino-obturator shelf (VOS)**
 - anchoring vagina to internal obturator fascia +/- iliopectineal line
 - horizontal suspension makes obstructive problems less common
- 2) laparoscopic colposuspension
 - transperitoneal vs extraperitoneal
 - number and type of suture, site of anchorage



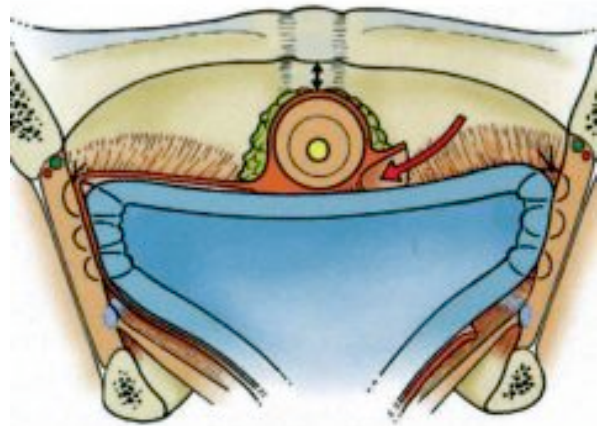
→ MMK



→ BURCH



→ PARAVAGINAL REPAIR



→ VAGINO-OBTURATOR SHELF (VOS)

ASSESSING OUTCOMES OF THERAPY

What are some key points to consider in assessing outcomes of Rx?

- 1) no data to support that ISD can influence outcomes or the type of surgical Rx
- 2) need to look at long-term f/u (>5yrs) results to see true benefits of better procedures
 - most are good in short-term (2yrs)
- 3) definition of “cure” must be scrutinized
 - free of SUI different from free of any incontinence
 - even N healthy women have spectrum of dryness (40% of nullips 30-50yrs old have some mild SUI with exercise)
- 4) must define expectations as “success” will be determined by patients’ pre-op expectations

INDICATIONS FOR RETROPUBIC REPAIR

What are the indications for a retropubic suspension for SUI?

- all women with SUI should have a trial of conservative Rx
- **ideal for women with SUI mainly due to urethral hypermobility**
- 1) patient undergoing laparotomy for concomitant abdominal Sx that can't be done vaginally
- 2) limited vaginal access

What are the contraindications to a retropubic suspension for SUI?

- 1) prior failed incontinence surgery with high likelihood of existing ISD
- 2) SUI solely due to ISD (ie fixed, nonfunctional proximal urethra)
- 3) pan-pelvic floor weakness
 - need combined alternative pelvic floor repair } especially for central cystocele, rectocele & introital deficiency
- 4) inadequate vaginal length or mobility (eg prior vaginal Sx or RADs)

Which approach is more successful for SUI, vaginal or retropubic?

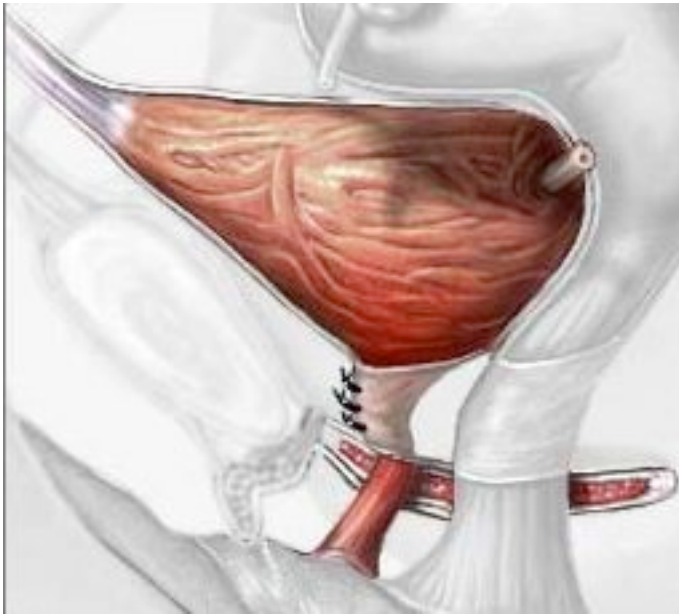
- similar success rates in short-term
- **retropubic approach has better long-term results than vaginal approach**
 - 60% success at 5yrs vs 40%
 - **PVS is only sling that was comparable long-term**
- retropubic approach is better for concomitant cystoceles } should be combined with sling
- vaginal approach is less morbid

GENERAL TECHNICAL ISSUES

What is the best approach to the retropubic dissection?

- supine, low dorsal lithotomy in stirrups
- Foley inserted
- Pfannenstiel or lower midline incision
- develop retroperitoneal space of Retzius
- identify BN, anterior vaginal wall, urethra
- identify lateral limits of bladder as it reflects off vaginal wall
- "roll" bladder medially off edge of vaginal wall
 - may need to open endopelvic fascia
- suspension performed with absorbable suture
 - some use non-absorbable
- urethral catheter or S/P tube x ~5days
 - S/P tube may be better } less infection, earlier resumption of N bladder function, easier to manage, can avoid CIC
- JP drain if concern about hemostasis

MARSHALL-MARCHETTI-KRANTZ PROCEDURE



What are the important steps in a MMK suspension for SUI?

- cystourethropexy procedure
- 3 sutures placed on either side of urethra through full-thickness vaginal wall (excluding mucosa) and **fixed to posterior aspect of pubic symphysis & adjacent periosteum**
- Marchetti modification is to omit urethral wall bite
- most proximal suture is at level of BN } often needs to be fixed to insertion of rectus muscle
- can also place additional sutures from anterior bladder wall and rectus muscles

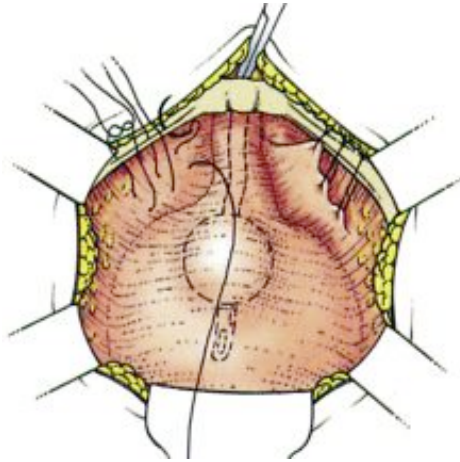
How successful is the MMK suspension for SUI?

- long term success rates range from 40-90% } not as durable as Burch

What are the potential complications specific to a MMK suspension for SUI?

- any complication can occur in up to 20%
- **osteitis pubis (1-3%)** } pubic pain radiating to inner thighs, worse with movement
Rx → bed rest, analgesics, +/- steroids
- worse incontinence } urethral tethering with sphincter dysfunction (posterior weakness)
- **retention**
- bladder stones from erosion if non-absorbable sutures into bladder
- *** **risk of osteitis pubis makes MMK a bad option now** ***

BURCH CULPOSUSPENSION



What are the important steps in a Burch colposuspension for SUI?

- 2-4 sutures placed through periurethral fascia & anterior vaginal wall (excluding mucosa) lateral to bladder edge and **fixed to Cooper's ligament (iliopectineal)**
 - sutures placed in mediolateral direction
 - sutures tied loosely } approximation to promote adhesion formation
- avoid urethral wall
- distal most suture placed at level of BN
- Ball-Burch modification } anterior urethral wall plicated at proximal and midurethra

How successful is the Burch colposuspension for SUI?

- long term success rates range from 70-90% } more durable than MMK
 - } higher cure rates than MMK
- **should be considered STANDARD open retropubic colposuspension**
- as effective as any other procedure in primary or secondary Sx at curing SUI

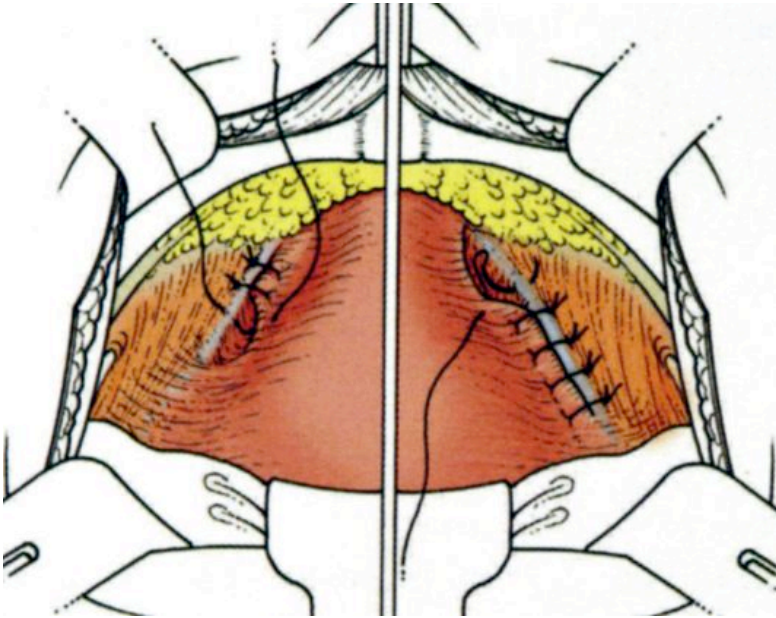
What are some predictors of Burch failure?

- re-do procedure
- urge incontinence
- low pressure urethra (controversial)
- sphincteric weakness

What are the potential complications specific to a Burch colposuspension for SUI?

- any complication can occur in up to 20%
- worsening of incontinence } may expose weakness of posterior wall and open BN
- **enterocele (5%)** } more common w/ Burch due to aggravation of post. wall weakness
 - prophylactic obliteration of cul-de-sac of Douglas decreases risk
- **post-colposuspension syndrome** (pain in one or both groins at site of suspension)
 - more common with Burch

PARAVAGINAL REPAIR



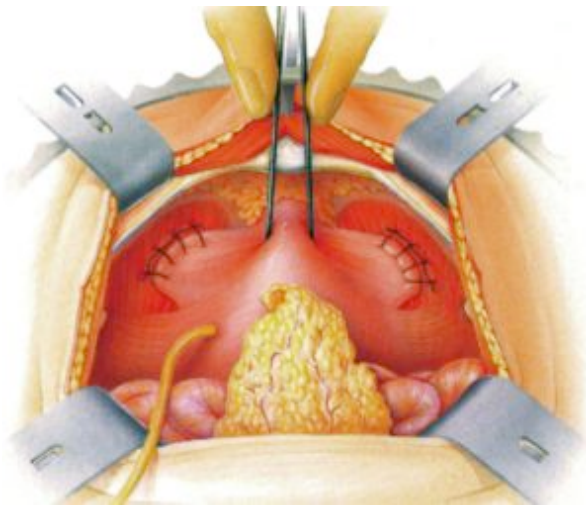
What are the important steps in a Paravaginal repair for SUI?

- bladder and urethra not mobilized from vaginal attachments
- 3-8 sutures placed through lateral vaginal sulcus + overlying fascia and then **fixed to arcus tendineus fasciae pelvis (ATFP)**
 - reattachment carried from back of lower edge of symphysis to ischial spine
 - at level of BN, suture is placed through paravaginal fascia & vaginal wall (excluding mucosa)
- ensure 3 fingers space between pubis and urethra to prevent rotational descent

How successful is the paravaginal repair for SUI?

- low short and long term success rates } 50-70% at ~1yr
- slightly less post-op retention } **less effective than other forms of colposuspension**

VAGINO-OBTURATOR SHELF REPAIR



What are the important steps in a vagino-obturator shelf repair for SUI?

- endopelvic fascia opened and inferolateral margin of bladder separated off obturator muscle
- sutures placed through full thickness of vagina and overlying endopelvic fascia and then **fixed to obturator muscle/fascia**
 - suture placement is above that in paravaginal repair
 - can even modify VOS by including bite of iliopectineal ligament (Cooper's) to add more elevation (similar to Burch)

How successful is the VOS repair for SUI?

- short and intermediate-term cure rates range from 60-80%
 - more clinical studies needed

LAPAROSCOPIC RETROPUBIC SUSPENSION

Which retropubic suspensions have been performed laparoscopically?

- MMK was first } Burch & paravaginal repair have also been performed
- modifications have included use of mesh, staples, fibrin sealant
 - extraperitoneal or transperitoneal approach

What are the advantages & disadvantages of a laparoscopic approach to retropubic suspensions for SUI?

→ ADVANTAGES

- improved visualization
- less post-op pain
- shorter hospital stay
- faster recovery
- less blood loss

→ DISADVANTAGES

- technically difficult
- longer OR times
- higher operative cost
- ?higher complication rate

How successful are laparoscopic retropubic suspensions for SUI?

- similar short term success to open approach
- **long term results not as good as open** } 50% cure/improvement rates at ~3-4yrs
- results better if more sutures used
- results better with sutures than staples or mesh

COMPLICATIONS OF RETROPUBIC REPAIRS

What are the potential complications following retropubic suspension procedures?

→ **overall complication rate ~20%**

→ general

- bleeding } 5% transfusion rate
- wound infection/dehiscence (5%)
- infection (4%)
- abscess formation
- GU organ injury (bladder, urethra, ureter)
- DVT/PE
- atelectasis/pneumonia

→ specific

- retention } may see new storage symptoms + retropubically angled & fixed urethra
 } risk of retention >4wks post-op is 5% & risk of permanent retention <5%
 Rx → revision with release of urethral into more anatomic position
- detrusor overactivity
- vaginal prolapse
- cystocele } central defect cystoceles not corrected with retropubic suspensions
- enterocele } more common w/ Burch due to aggravation of post. wall weakness (5%)
 → prophylactic obliteration of cul-de-sac of Douglas decreases risk
- de novo urgency } may be related to BOO
- voiding dysfunction
- post-colposuspension syndrome (pain in one or both groins at site of suspension)
 → more common with Burch
- osteitis pubis
 → most common after MMK

How common is detrusor overactivity in SUI?

→ **~30% concomitant rate of DO with SUI**

- most storage symptoms resolve after surgery
- no difference in incidence rates between types of suspension

Rx → behaviour modification + anti-muscarinics

- intravesical botox
- neuromodulation
- detrusor myomectomy
- augmentation cystoplasty

COMPARISONS BETWEEN INCONTINENCE PROCEDURES

Which retropubic suspension is best for SUI?

- **Burch slightly better cure rates cf MMK** } MMK also has unacceptable risk of very morbid osteitis pubis (1-3%)
- Burch much better than Paravaginal repair (limited data though)

How does retropubic suspension for SUI compare to other SUI procedures?

- more effective than needle suspensions or anterior colporrhaphies } 85% vs 50-70%
- **similar outcomes to PVS** although may have less post-op voiding issues than PVS
- **similar long-term success rates as TVT but TVT is much less invasive**

Chapter #66 – Vaginal Reconstructive Surgery for Sphincteric Incontinence & Prolapse

EPIDEMIOLOGY OF URINARY INCONTINENCE, ANAL INCONTINENCE, AND PELVIC ORGAN PROLAPSE

What is the prevalence of urinary incontinence?

- varies widely and depends on definition of incontinence and population studied
- more common with increasing age
- SUI more common in young and middle aged women
- mixed & urge incontinence more common in older women
- less common with stricter definitions of incontinence
 - 5% daily incontinence in women <60yrs
 - 5-20% daily incontinence in women >65yrs

How common is anal and fecal incontinence?

- true prevalence is difficult to ascertain
- anal incontinence prevalence is 2-25% } flatus or feces
- fecal incontinence prevalence is 1-20% } feces only

What is pelvic organ prolapse?

- downward descent of pelvic organs resulting in protrusion of vagina and/or uterine cervix
- does not include rectal prolapse
- prevalence ranges from 20-40% } depending on age
- lifetime risk of needing an operation for prolapse is ~10%

What are the RFs for SUI & pelvic organ prolapse (CHART)?

SUI	POP
<ul style="list-style-type: none"> - aging - pregnancy & parity - vaginal delivery - obesity - previous pelvic surgery - constipation - smoking - heavy lifting (debatable) - genetics (Hispanics have highest risk) - chronic cough or lung disease - bladder exstrophy 	<ul style="list-style-type: none"> - aging - pregnancy & parity - vaginal delivery - obesity - previous pelvic surgery - constipation - smoking - heavy lifting (debatable) - genetics (Hispanics have highest risk) - hysterectomy

→ role of episiotomy is unclear & controversial

→ menopause is not a RF for SUI or pelvic organ prolapse

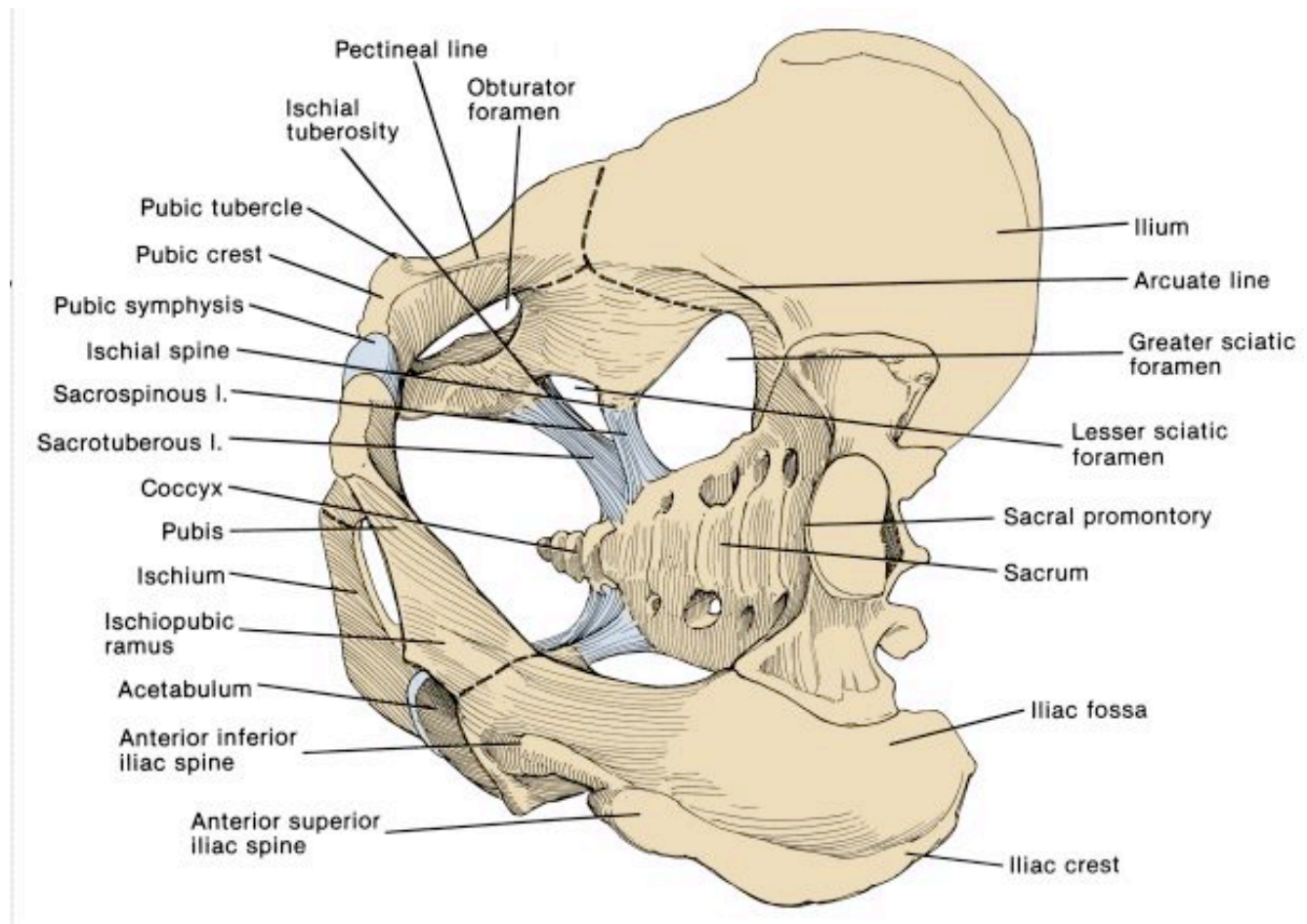
ANATOMY OF PELVIC FLOOR, SUPPORTING STRUCTURES, AND PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE

What are the bones of the pelvis?

- 1) sacrum
- 2) ilium
- 3) ischium
- 4) acetabulum

What is the difference between the true and false pelvis?

- true → contents below arcuate line (sacral promontory to pectineal-line)
- false → formed by the iliac fossae and largely in contact with intraperitoneal contents



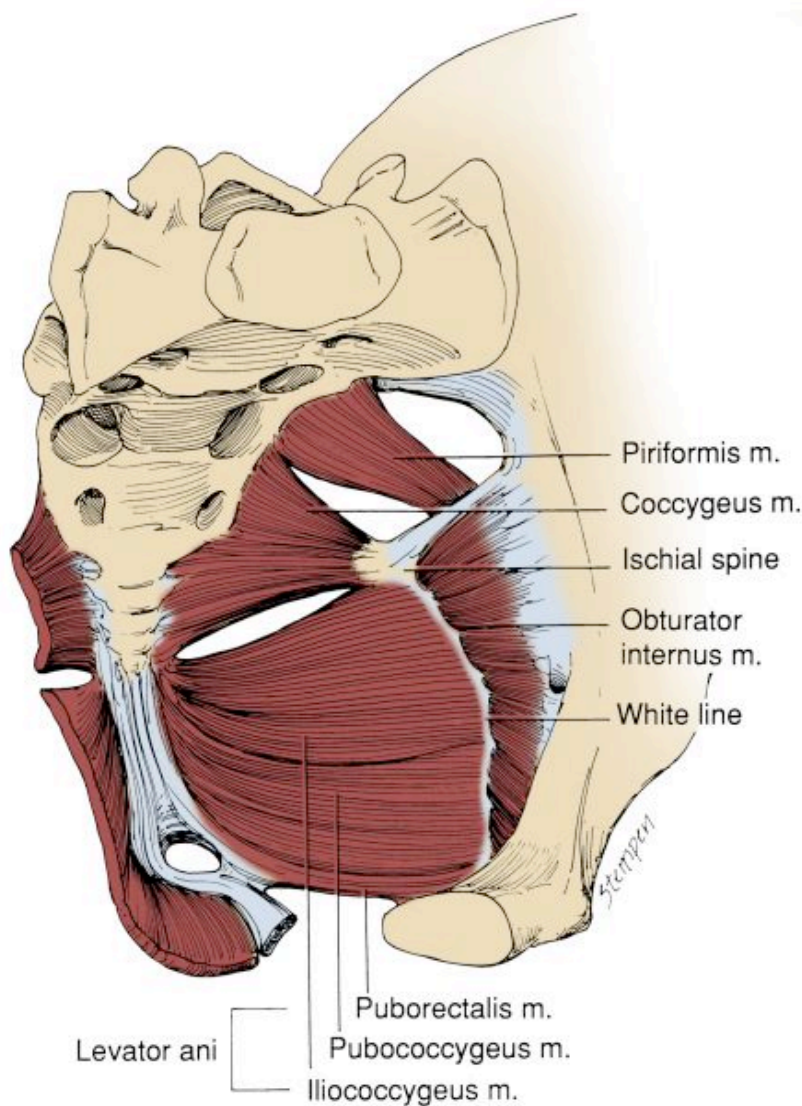
What structures give strength to the SI joint?

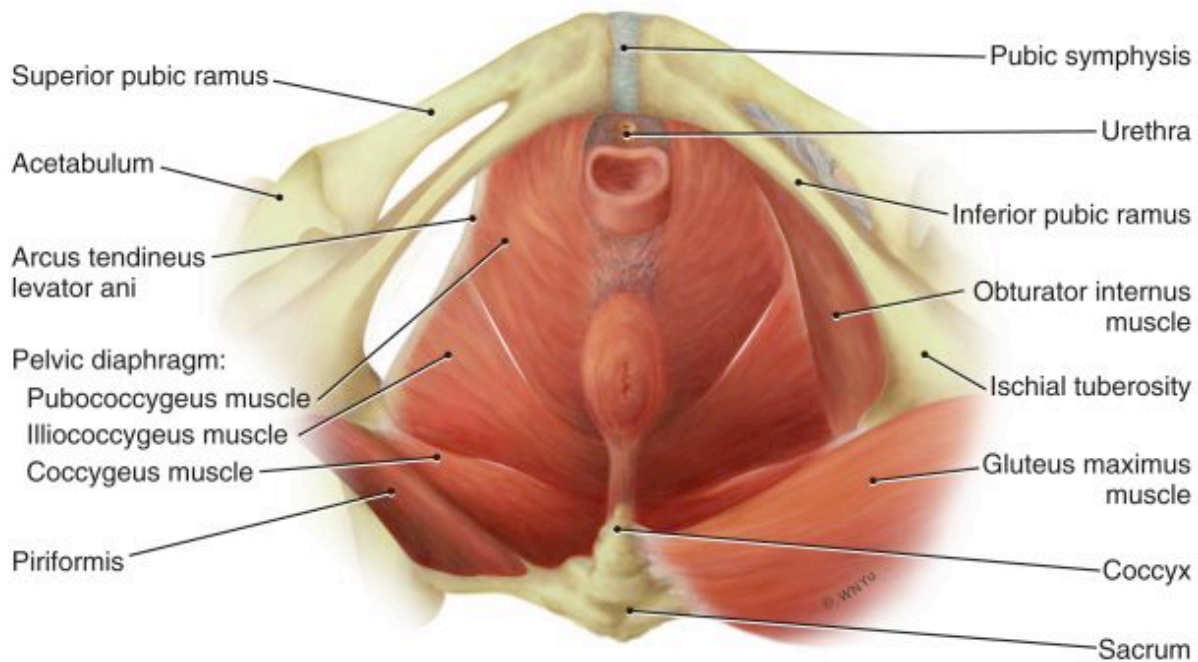
- sacrospinous ligament → ischial spine to sacrum (separates greater and lesser sciatic foramen)
- sacrotuberous ligament → ischial tuberosity to sacrum
- anterior and posterior ligaments

Name the main muscles of the pelvic diaphragm?

- 1) Obturator internus → from inner obturator foramen, through lesser sciatic foramen, to femur
→ fascia overlying this muscle forms tendinous arc (origin of levators)
- 2) Levator ani → pelvic diaphragm muscles which contain a hiatus anteriorly
- urethra, vagina, rectum pass through UG hiatus
→ iliococcygeus
→ pubococcygeus
→ puborectalis
} fusion of these forms horizontal **levator plate** between
anus and coccyx
- 3) coccygeus → ischial spine/sacrospinous ligament to lateral border of sacrum and coccyx
- 4) piriformis → from lateral aspect of sacrum, passes through and fills greater sciatic foramen

***** weakness of levator ani may loosen sling behind anorectum and lead to sagging of levator plate, opening UG hiatus and predisposing to pelvic organ prolapse *****





Describe the pelvic fascia.

- contains collagen, but also smooth muscle & elastic tissue (may have role in support AND function)
- continuous with retroperitoneal fascia
- contains 3 layers:
 - 1) outer → **endopelvic fascia**
 - lines inner surface of pelvic muscles
 - **continuous with transversalis fascia layer**
 - fixed to arcuate line of pelvis, Cooper's ligament, sacrospinous ligament, ischial spine, and tendinous arc of levator ani
 - 2) intermediate → embeds pelvic viscera in a fatty, compressible layer that is easily swept away to expose deeper potential spaces
 - contains all pelvic vessels and some pelvic nerves
 - 3) inner → lies just beneath peritoneum, covering rectum & dome of bladder, to form Denonvilliers' fascia

What are the 3 most important components of the pelvic fascia?

- 1) anteriorly → **puboprostatic ligaments** } attaches to lower 5th of pubis, lateral to symphysis and to jxn of prostate and external sphincter
 - **pubourethral ligaments** in women } insert on proximal 3rd of urethra
- 2) laterally → **arcus tendineus fascia pelvis (ATFP)** extends from puboprostatics (pubourethrals) to ischial spine
 - forms at jxn of endopelvic and visceral fascia
 - significant in SUI, urethroceles, cystoceles
- 3) posteriorly → fans out laterally from rectum to pelvic side wall as **lateral & posterior vesical ligaments**
 - **cardinal & uterosacral ligaments** in women

What is the difference b/w the arcus tendineus of levator ani (ATLA) and arcus tendineus fascia pelvis (ATFP)?

- ATLA } pubic ramus to ischial spine
→ where obturator fascia, superior & inferior diaphragmatic fasciae, and degenerated aponeurosis of levator ani fuse
- ATFP } lower part of symphysis pubis to ischial spine
→ fascial supports of bladder & upper urethra and vagina attach to ATFP

What are the 2 urethral supports in the “double hammock”?

- 1) anterior vaginal wall suspended to levators (pubococcygeus muscle)
- 2) anterior vaginal wall suspended by endopelvic fascial attachments to ATFP

What are the 4 causes of anterior vaginal wall prolapse?

- 1) central weakness } cystocele from central defect
- 2) **weakness of lateral attachments to ATFP** } cystocele from lateral or paravaginal defect
→ **most common (seen in ~80%)**
- 3) proximal transverse defect } separation of anterior wall fascia from ring of fascia around cervix
- 4) distal defect } separation of pubocervical fascia from pubis

What are the structures involved in pelvic organ support?

- 1) anterior supports } puboprostatic/pubourethral ligaments
} double hammock (anterior vaginal wall to levators and to ATFP)
- 2) middle supports } cardinal and uterosacral ligaments
- 3) posterior supports } paracolpium (posterior vaginal wall to rectovaginal fascia and pelvic diaphragm)
} rectovaginal fascia (equivalent of endopelvic fascia in this area) extends from perineal body toward the ATFP

Where is the weakest point in the pelvic floor?

- urogenital hiatus

Describe the urogenital diaphragm.

- triangular in shape; from pubis to ischial tuberosities
- perineal membrane lies at center of UG diaphragm and defines it
- ends abruptly posteriorly w/ superficial & deep transverse perinei running along its free edge
- external genitalia attach to its inferior surface
- superiorly it supports urethral sphincter
- perineal body represents point of fusion between free edge of UG diaphragm and posterior apex of urogenital hiatus

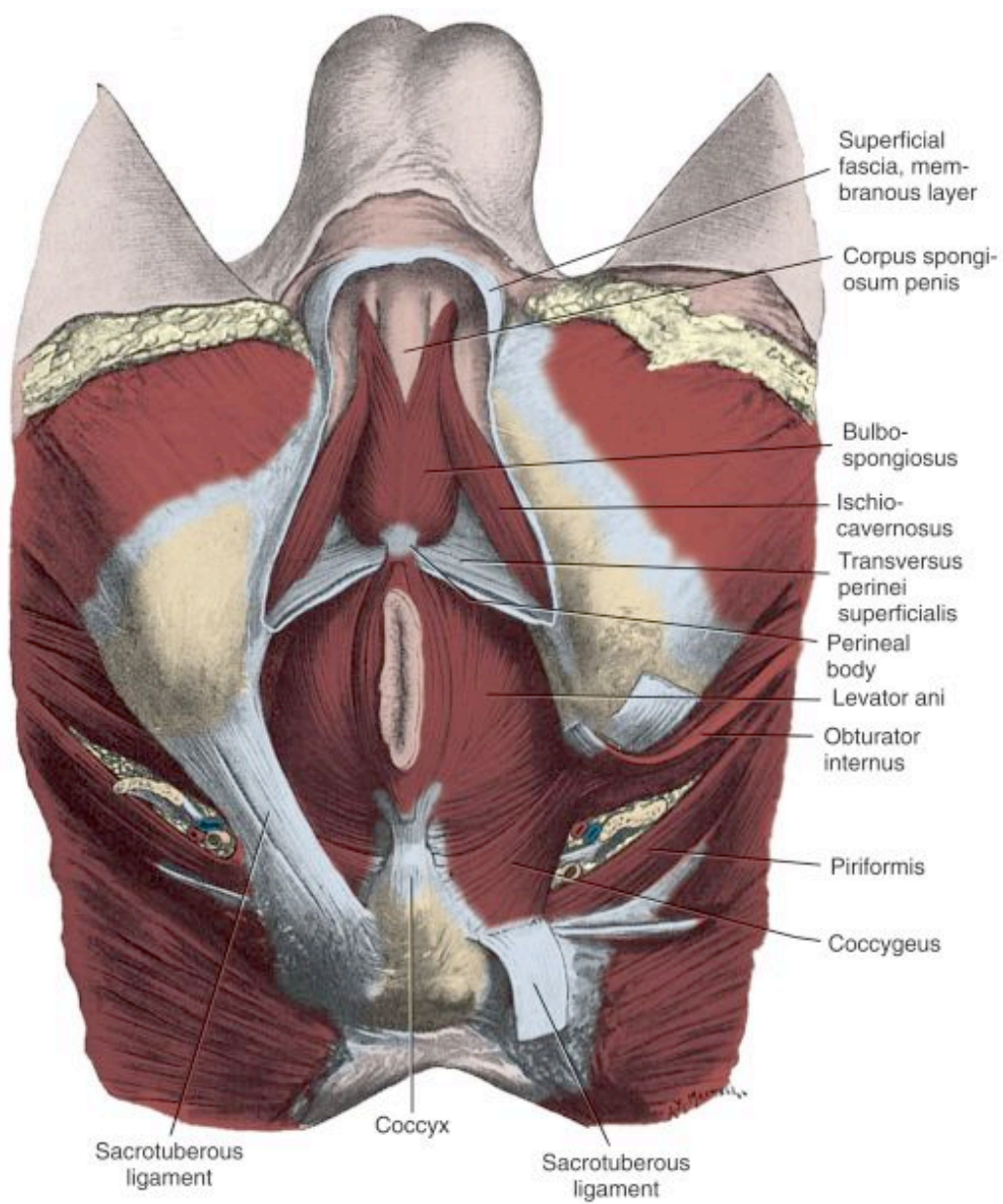
What is the main innervation of the levator ani?

- primarily S3-S4 via pudendal nerve
- mostly slow-twitch (type 1) fibers in levators
- some fast-twitch (type 2) fibers in mainly periurethral and perianal areas

Which muscles insert into the perineal body?

- pyramid-shaped structure is the key to pelvic support
- almost every pelvic muscle inserts into perineal body (6) }}} “TREBLE”
 - **Transverse perinea (superficial & deep)**
 - **Rectourethralis**
 - **EUS**
 - **Bulbospongiosus**
 - **Levator ani**
 - **External anal sphincter**
- most pelvic fascia also insert into the perineal body (4) }}} “D-PEC”
 - **Denonvilliers’**
 - **Endopelvic fascia**
 - **Perineal membrane**
 - **Colles’**

*** weakness of perineal body results in elongation, predisposing to defects such as rectocele & enterocele ***



PELVIC ORGAN PROLAPSE

What are the natural protective structures that prevent pelvic organ prolapse?

- 1) endopelvic fasciae & suspensory ligaments (cardinal, uterosacral)
→ attach uterus & vagina to pelvic wall
- 2) levator ani muscles
→ constrict GU hiatus and organs within
- 3) levator plate
→ closed & suspended organs rest on surface and act as a flap valve

What are the 3 different levels of pelvic weakness that predispose to pelvic organ prolapse?

- level 1 (apical) } loss of N support of upper paracolpium & parametrium
→ associated w/ uterine prolapse, vaginal vault prolapse, +/- enterocele
- level 2 (mid vaginal) } anterior defects
→ associated w/ cystocele +/- hypermobile urethra
} posterior defects
→ associated w/ rectocele
- level 3 (distal vaginal) } weakness of lower vagina or perineum
→ associated w/ urethral hypermobility, perineal defects, rectocele

What is the anatomic classification of pelvic organ prolapse (CHART)?

→ **clinical correlation between pelvic symptoms and extent of prolapse is weak**

- **many have no symptoms, especially if prolapse remains inside vagina**

→ **ANTERIOR vaginal wall (anterior compartment)**

- 1) cystocele } central weakness = posterior cystocele
} lateral weakness = anterior cystocele
} combined
- 2) urethrocele (hypermobility)

→ **APICAL vaginal wall (middle compartment)**

- 1) enterocele } anterior (between vagina and bladder)
} lateral (pudendal)
} posterior (between vagina and rectum – most common)
- 2) uterine prolapse
- 3) uterovaginal prolapse +/- cystocele, enterocele, rectocele
→ most common to have cystocele and rectocele without enterocele
- 4) vaginal vault eversion (post-hysterectomy) +/- cystocele, enterocele, rectocele
→ 75% have enteroceles

→ **POSTERIOR vaginal wall (posterior compartment)**

- 1) rectocele } low (disruption of distal vaginal)
} midvaginal (loss of lateral supports or defect in rectovaginal septum)
} high (loss of lateral or apical vaginal supports or defect in rectovaginal septum)

→ **PERINEAL BODY defects**

- frequently associated with other organ prolapse

What are the 4 different types of enteroceles?

- 1) congenital } posterior
→ failure of fusion or reopening of fused peritoneal leaves in cul-de-sac
- 2) “pulsion” } from pushing with increased Pabdo
→ post-hysterectomy
→ failure to reapproximate superior aspects of pubocervical & rectovaginal fascia
- 3) “traction” } from pulling down of vault by prolapsing organs
→ associated with cystocele and rectocele
- 4) iatrogenic } after surgery that changes vaginal axis (eg Burch)
→ from widening of entry into cul-de-sac

List the classical grading system for cystoceles (OLD)

- grade 1 } mild (protrudes slightly into vagina)
- grade 2 } moderate (prolapsed bladder reaches vaginal opening)
- grade 3 } severe (prolapsed bladder is outside vagina)

List potential complications related to a grade 3 cystocele.

- urinary retention
- urinary incontinence
- ureteral obstruction
- LUTS
- recurrent UTIs
- bladder stones
- pain/pressure
- sexual dysfunction (eg dyspareunia)
- bowel dysfunction

What is involved in the initial w/u of incontinence/pelvic organ prolapse?

- 1) History } characterize any incontinence
 - frequency, severity, type, degree of bother, effect on QOL, precipitants, previous treatment to date, pad use, etc
 - } **need to assess lower GU tract, bowel fxn, sexual fxn, & local symptoms**
 - LUTS } frequency, urgency, nocturia, weak stream, intermittency, straining, emptying
 - } hx of UTIs, AUR, hematuria, etc
 - anal incontinence, difficulty defecating/constipation
 - dyspareunia, decreased desire most common
 - local symptoms include vaginal pressure/heaviness, vaginal/perineal pain, low back pain, abdo pressure or pain, palpable bulge/mass
 - } **voiding diary (3 days optimal), fluid intake habits, pad tests, questionnaires**
 - } ask about RFs for incontinence + r/o causes of transient incontinence
 - vaginal deliveries, obese, poor nutrition, smoker, activity level, etc
 - DIAPPERS
 - } PMHx (eg stroke, MS, SCI, RADs, menses, etc)
 - } PSHx (APR, hysterectomy, RP, etc)
 - } meds, allergies, drugs
- 2) P/E } neurologic exam (gait, perineal sensation, bulbocavernosus reflex, cognitive status)
 - } abdo exam (distended bladder, masses, hernias, DRE, etc)
 - } female pelvic exam (vaginal atrophy, skin excoriation, vault exam, organ prolapse, pelvic floor muscle strength, cough test, Q-tip test, Marshall test, +/- dye tests)
 - **need to r/o prolapse associated w/ occult or masked SUI**
 - lithotomy and standing exams
 - if incontinence not demonstrable in lithotomy, repeat in standing position
 - Q-tip test = urethral hypermobility
 - Marshall test = anterior vaginal wall
 - **anterior, apical/middle, and posterior compartment**
 - also assess rectovaginal septum, perineal body, anal sphincter, pelvic floor muscles
- 3) routine lab tests } urinalysis, urine C&S, +/- cytology +/- serum creatinine
- 4) initial investigations } uroflow + PVR
- 5) (WHEN INDICATED) additional testing } cystoscopy + UDS + imaging + EMG
 - CMG } detrusor overactivity, low compliance, VLPP, DLPP
 - PFS } high pressure + low flow, low pressure + low flow
 - } BOOI >40 is obstruction [$P_{det}Q_{max} - 2(Q_{max})$]
 - } BCI <100 is poor contractility [$P_{det}Q_{max} + 5(Q_{max})$]

List 4 primary clinical areas that need to be assessed in patients with pelvic organ prolapse?

- 1) lower urinary tract
- 2) bowel function
- 3) sexual function
- 4) local symptoms

How common is urinary incontinence in women with pelvic organ prolapse?

- many RFs for urinary incontinence are also RFs for pelvic organ prolapse
- as prolapse worsens, stress incontinence often improves
- reduction of vaginal prolapse with pessary or speculum can produce SUI in up to 80%

What is a good questionnaire for symptom assessment (CHART)?

→ UDI, UDI-6, BFLUTS. ICIQ

→ eg UDI-6 } Do you experience, and, if so how much are you bothered by:

- 1) frequency
- 2) urgency incontinence
- 3) SUI
- 4) small amounts of urine leakage
- 5) difficulty emptying your bladder
- 6) pain or discomfort in lower abdomen or genital area

What is a good questionnaire for assessment of impact on QOL (CHART)?

→ IIQ, IIQ-7, I-QoL, King's Health Questionnaire, UISS

→ eg IIQ-7 } Has urine leakage and/or prolapse affected your:

- 1) ability to do household chores (cooking, cleaning, laundry)
- 2) physical activity (walking, swimming, other exercise)
- 3) entertainment activities (movies, concerts)
- 4) ability to travel by car or bus >30mins from home
- 5) social activities outside your home
- 6) emotional health (nervousness, depression)
- 7) feeling frustrated

How common is obstruction in women with pelvic organ prolapse?

- **common with severe prolapse** } degree of obstruction may correlate with severity of prolapse
- may need to reduce prolapse to void (splinting)
- $Q_{max} \leq 12 \text{ cc/s}$ + P_{det} at max flow $\geq 25 \text{ cm H}_2\text{O}$ + clinical suspicion has good predictive value
- prevalence of hydronephrosis is low

How common is anal incontinence in women with pelvic organ prolapse?

- found in up to 30%
- most common cause of anal incontinence is obstetric trauma (direct injury to anal sphincter and/or damage to motor innervation to pelvic floor)

Classify female sexual dysfunction (CHART)? } } } “ I don’t want it ... I’m not horny ... I can’t cum ... it hurts”

→ 1999 Consensus Classification (**now there's an updated, more in depth, classification '04**)

- [illegible]

What is the clinical classification of pelvic organ prolapse?

→ made by ICS committee 1996 } Pelvic Organ Prolapse Quantification (POPQ)

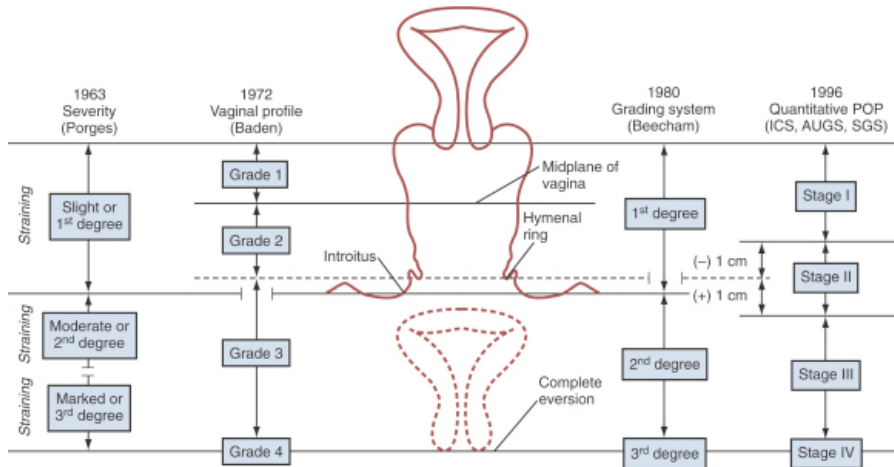
- relates 6 points in vagina (2 anterior, 2 posterior, 2 apical) **in relation to hymenal ring**

→ measurements taken with patient in dorsal lithotomy & straining

→ does not identify unilateral or asymmetrical defects

- **stage 1** } most distal portion of prolapse is **>1cm above level of hymen**
- **stage 2** } most distal portion of prolapse is **within 1cm of hymenal plane (above or below)**
- **stage 3** } most distal portion of prolapse protrudes **>1cm below level of hymen BUT protrudes no farther than 2cm less than the total vaginal length**
- **stage 4** } **vaginal eversion** is essentially complete

→ other classifications include Porges (severity - introitus), Baden (vaginal profile – hymenal ring), Beecham (cervical - introitus)

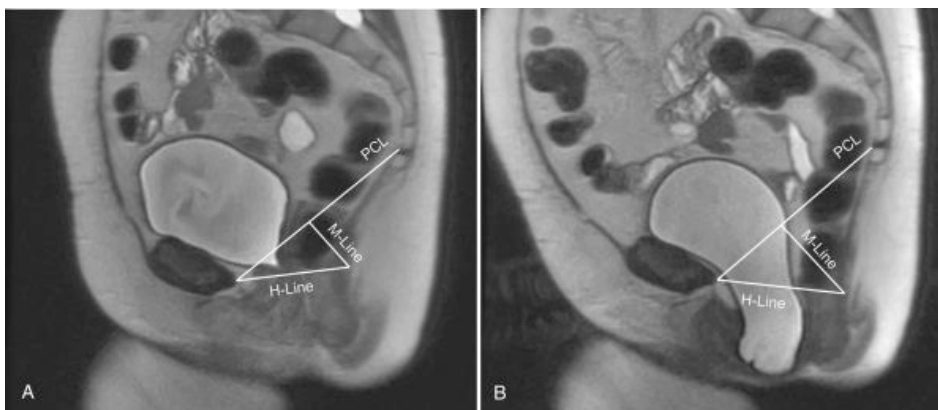


What are the indications for additional testing (UDS, cysto, etc) in incontinence/prolapse?

- hematuria without UTI
- abN PVR
- complex presentation where more precise information is desired
- patients with known or suspected voiding phase dysfunction that may affect Rx
- patients with known or suspected neurologic disorder that may affect bladder or sphincter
- unable to demonstrate incontinence clinically despite patient complaints
- Rx with potential for significant morbidity
- failure of empiric Rx
- hx of anti-incontinence or lower urinary tract reconstructive surgery
- hx of radical pelvic surgery (APR, etc)
- hx of high dose RADs to pelvis
- hx of urogenital or pelvic surgery + symptomatic pelvic prolapse

What is the role of MRI in patients with incontinence or pelvic organ prolapse?

- may be more accurate than P/E in Dx'ing prolapsed organs } STILL INVESTIGATIONAL
- can assess **organ prolapse, BN anatomy, assessment of levator ani, evaluation of SUI**
- common view is T2 sagittal midline image showing symphysis, BN, vagina, rectum, & coccyx
 - resting and straining images
- PCL, H line, M line
- **MRI detects more enteroceles but fewer rectoceles (unless rectal contrast used)**



→ T2 MRI of PELVIC PROLAPSE

- H line = size of levator hiatus (pubis to posterior anal canal – puborectal line)
- M line = amount of levator descent from pubococcygeal line (PCL to H line)

VAGINAL SURGERY FOR STRESS INCONTINENCE

What are the management options for SUI caused by sphincteric dysfunction?

- 1) behavioural Rx } bladder training (timed voiding, etc), Education, Habit changes (fluid intake, caffeine, bowel habits, etc), Voiding diary
- 2) pelvic floor muscle training } Kegels, biofeedback, vaginal cones, electrical stimulation
→ RCT shows PFMT is better than no treatment for SUI
→ no added benefit of biofeedback + PFMT
- 3) oral meds } α -agonists (increase urethral muscle tone eg ephedrine, PPA, midodrine)
→ only weak evidence showing they are better than placebo
} SNRIs (eg duloxetine)
} TCAs (eg imipramine)
- 4) pessaries } for prolapse related SUI
- 5) topical meds } estrogen → LIMITED TO NO ROLE FOR SUI
- 6) urethral bulking agents } collagen, PTFE, hyaluronic acid/dextranomer (Zuidex/Deflux), polydimethylsiloxane elastomer (Macroplastique)
→ short-duration of effect
- 7) surgery } **PVS & midurethral slings**
} **urethral culposuspension (open vs laparoscopic)**
} **needle suspension**
} **AUS**
} **vaginal anterior repair (anterior colporrhaphy)**
- 8) diversion } only considered for refractory cases with severe sphincteric damage

How do transvaginal needle suspensions compare to retropubic suspensions?

- less peri-op morbidity
- equivalent short-term cure (dry) rates
- **worse long-term outcomes** cf retropubic suspensions and slings } 70% dry at 4yrs (vs ~85%)
→ indicated in F w/ mild SUI, less ISD & those willing to compromise LT benefit for lower immediate M&M
→ **limited role now with midurethral slings**

What is the peri-op management of patients undergoing vaginal suspensions?

- antibiotic prophylaxis controversial
- dorsal lithotomy + Trendelenburg
- weighted vaginal speculum or Simms retractor + Scott retractor to spread labia
- Foley to decompress bladder and identify BN
- injection of saline to raise submucosal bleb
- intra-op cysto to r/o bladder perforation or urethral injury
- post-op Foley or S/P tube +/- vaginal packing x 24hrs

List the different transvaginal needle suspensions performed

- 1) modified Pereyra } pass needle from lower abdo incision through to periurethral area after T-shaped vaginal incision (modification includes BN plication)
- 2) Stamey } Stamey needle passed through 2 lateral suprapubic incisions into periurethral space
} non-absorbable sutures + Dacron pledgets on vaginal side to buttress sutures
} S/P tube insertion + cystoscopy
- 3) Raz } U-shaped vaginal incision with entrance into retropubic space sharply
} passage of ligature carrier from abdomen down to vaginal incision
} S/P tube
- 4) Gittes } Stamey needle passed twice through 2 lateral suprapubic stab incisions down through vaginal wall at BN and sutures tied over rectus fascia without tension
→ “no incision” technique } sutures cut through vaginal wall & become buried in scar (“auto- pledget”)
} S/P tube + cystoscopy
} **worst outcomes of the vaginal suspensions**

What are the potential complications of vaginal suspensions for SUI?

- intra-op } bleeding (risk of transfusion is ~1%)
 - } suture passage through bladder
 - } laceration of bladder or urethra during dissection
- post-op } urinary retention (persists >2wks in ~5%)
 - } de novo urgency (storage symptoms) occurs in 5-15%
 - } persistent pelvic pain or dyspareunia (5%)
 - } pelvic organ prolapse (6%)

VAGINAL SURGERY FOR PROLAPSE

What are the common terms used for vaginal and pelvic surgery?

- colporrhaphy = repair of vaginal wall
- colpocleisis = obliteration of vaginal lumen (denudation of mucosal strips then approximation of anterior & posterior walls)
- colpectomy = resection of vagina
- colpopexy = suspension of vaginal wall
- culdotomy = incision into (posterior) cul-de-sac (pouch of Douglas)
- culdoplasty (culdeplasty) = surgical obliteration of cul-de-sac to treat or prevent enterocele
 - abdominal } Moschowitz = multiple purse-string sutures picking up uterosacral ligaments laterally, posterior vaginal wall, and shallow bites of rectal serosa
 - } Halban = 3-4 parallel sagittal sutures starting on posterior vaginal wall picking up peritoneum and rectal serosa
 - vaginal } McCall = transverse sutures placed into cardinals, uterosacrals, pararectal fascia, peritoneum, and rectal serosa
- perineorrhaphy = repair of perineal body

What are the goals of surgery for pelvic organ prolapse (CHART)?

- 1) relieve symptoms
- 2) maintain or improve urinary, bowel, and sexual function
- 3) reposition pelvic structures and supports to normal anatomy
- 4) prevent new pelvic support defects and symptoms
- 5) correct concomitant intrapelvic disease
- 6) achieve a durable result

What are some non-surgical management options for pelvic organ prolapse?

→ to help alleviate symptoms and prevent worsening BUT actual hernia will not disappear

- 1) RF reduction
 - weight loss
 - stop smoking
 - address chronic cough
 - treat and prevent constipation
 - stop heavy lifting
- 2) vaginal estrogen } mainly to prepare vaginal tissues for surgery
→ 6wks pre-op course of vaginal cream
- 3) pelvic muscle exercises
- 4) pessaries } ring type \ may unmask SUI
 } support type / in ~20%

What are the characteristics of the ideal synthetic material to be used for pelvic organ prolapse Sx?

- biocompatible
- inert
- lack of allergic or inflammatory response
- sterile
- non-carcinogenic
- resistant to mechanical stress or shrinkage
- available in convenient and affordable format
- should not result in erosion or infection

What types of prosthetic MATERIALS are used for pelvic organ prolapse surgery?

- 1) autologous } vagina, abdo wall, thigh
 - morbidity of harvest site
 - use of inherently weak tissue
- 2) allograft } irradiated fascia lata
 - no harvest site morbidity
 - no increased risk of erosion associated with synthetics
 - small risk of antigenic expression and transmission of prions or HIV
- 3) xenograft } acellular porcine SIS, porcine dermis, bovine pericardium
 - small risk of animal zoonoses
- 4) synthetic } 4 types based on material, fiber type, and pore size
 - risk of erosion
 - risk of extrusion } inadequate incision closure, superficial placement, atrophy, infection
 - most grafts shrink by ~20%

What are the 4 different types of SYNTHETIC GRAFTS used for pelvic organ prolapse surgery?

- type 1 } polypropylene + monofilament + macropore (**prolene, surgipro, marlex**)
 - **lowest risk of erosion (<3%)**
 - lower rate of infection
 - most commonly used
- } polyglactin (vicryl), polyglycolic acid (dexon) + multifilament + macropore
- type 2 } expanded PTFE + multifilament + micropore (Gore-Tex)
 - multifilament fibers have higher risk of infection due to small interstices (<10µm) that allow bacteria but not leukocytes/macrophages
- type 3 } polyethylene + multifilament + micro/macropore (Mersilene)
- type 4 } polypropylene sheet + monofilament + submicropore (Cellgard)

How does synthetic graft erosion usually present?

- asymptomatic
- discharge
- dyspareunia
- vaginal pain

Anterior Vaginal Wall (anterior compartment)

What are the 4 causes of anterior vaginal wall prolapse?

- 1) central weakness } cystocele from central defect
 - accounts for only 1-2%
- 2) **weakness of lateral attachments to ATFP** } cystocele from lateral or paravaginal defect
 - **seen in 80-85%**
- 3) proximal transverse defect } separation of anterior wall fascia from ring of fascia around cervix
 - seen in 15% of patients
- 4) distal defect } separation of pubocervical fascia from pubis

What are the different ANTERIOR compartment procedures for POP?

→ CENTRAL, LATERAL, COMBINED CYSTOCELES

1) vaginal anterior colporrhaphy (central defects)

→ for cystoceles from central defects

→ in combination w/ other SUI procedures to address anterior midline support defects

→ not recommended for SUI (high failure rate ~50%)

- development of anterior submucosal layer and imbrication

- better outcomes with use of polyglactin mesh (placed over midline plication)

→ 5-20% recurrence rate

2) abdominal repair (lateral and combined defects)

→ paravaginal repair OR Burch colposuspension

→ 5-25% recurrence rates

3) vaginal paravaginal repair (lateral and combined defects)

- retropubic space developed and sutures placed from ATFP laterally to pubocervical fascia medially

- high complication rate

→ ~25% recurrence rate

4) 6-corner suspension (lateral and combined defects)

- similar to simple needle suspension + additional proximal sutures to support bladder

→ 10-20% recurrence rate

What are some combined procedures used for SUI + pelvic organ prolapse?

1) anterior colporrhaphy + needle BN suspension

→ SUI + moderate to large cystoceles

- goal post incision with distal limbs starting at midurethra and midline incision carried to anterior fornix of cervix

- colporrhaphy (+/- mesh graft) is combined with needle suspension

→ 7-15% SUI recurrence rate

→ 5-50% cystocele recurrence rate

2) anterior colporrhaphy + sling

→ SUI + cystocele

- colporrhaphy (+/- mesh graft) is combined with PVS/TVT } ?sequence of procedures (unclear)

→ 10-15% SUI recurrence rate

→ 10-25% cystocele recurrence rate

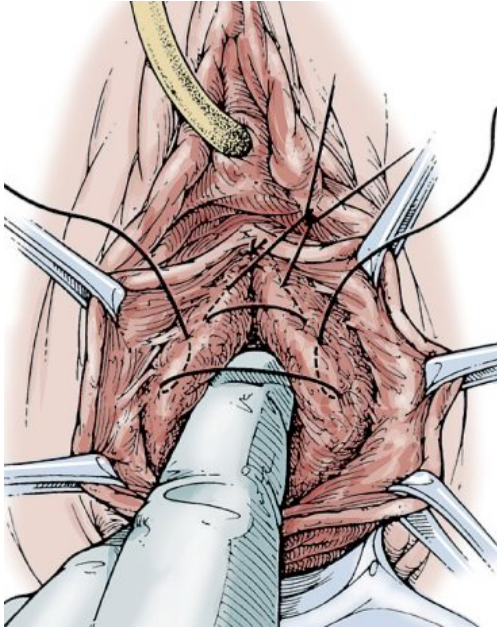
What are the potential complications of anterior vaginal colporrhaphy for POP?

- recurrence of cystocele
- de novo SUI or urgency incontinence
- bladder injury
- urethral injury
- bleeding
- urinary retention
- ureteral obstruction
- if used, graft erosion

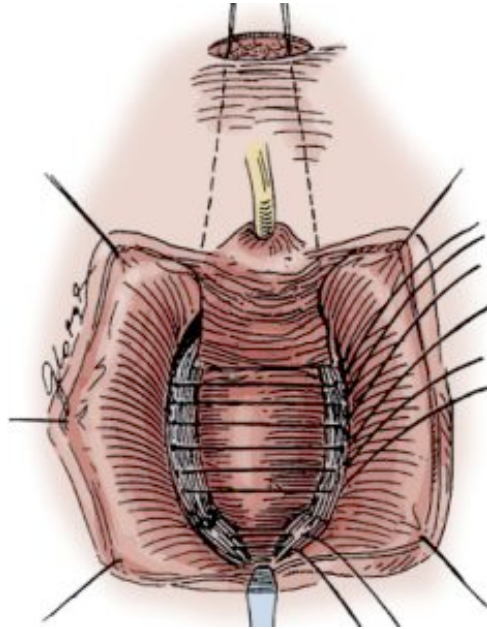
What are the potential complications of a vaginal paravaginal repair for POP?

→ higher complication rates

- bleeding, hematoma } transfusion rate 5-15%
- ureteric obstruction
- vaginal abscesses
- transient piriformis muscle syndrome
- femoral nerve paresis



→ ANTERIOR COLPORRHAPHY



→ ANTERIOR COLPORRHAPHY
+ NEEDLE BN SUSPENSION

Apical Vaginal Wall (Middle compartment)

What are the 3 causes of apical vaginal wall weakness?

- 1) weakness of cardinal & uterosacral ligaments
- 2) failure to reapproximate superior aspects of pubocervical & rectovaginal fascia at time of hysterectomy
- 3) widening of cul-de-sac from ventral fixation of vagina (eg post-Burch)
 - enterocele } anterior (b/w vagina & bladder), posterior (b/w vagina & rectum – most common), lateral (pudendal),
- uterine prolapse
- uterovaginal +/- cystocele, enterocele, rectocele
 - most common to have cystocele + rectocele without enterocele
- vaginal vault eversion (post-hysterectomy) +/- cystocele, enterocele, rectocele
 - 75% have enteroceles

What are the goals of enterocele repair procedures?

- 1) recognize the enterocele and its probable cause
- 2) expose, dissect, mobilize, and then excise or obliterate the entire sac
- 3) occlude orifice of sac by ligation as high as possible
- 4) perform all indicated repairs to provide adequate support from below for the occluded sac by reestablishing continuity of anterior & posterior vaginal fascia at apex and a N upper vaginal axis

What are the goals of uterine prolapse procedures?

- 1) vault suspension +/- hysterectomy +/- colporrhaphy
 - uterine descent is result of prolapse, NOT a cause of it } ie hysterectomy alone is not adequate
- 2) address enteroceles when indicated
- 3) repair coexisting anterior & posterior prolapse
- 4) perform anti-incontinence procedures as needed

What are the different MIDDLE compartment procedures for POP?

→ ENTEROCELE, UTERINE PROLAPSE, VAGINAL VAULT PROLAPSE

1) vaginal enterocele repair

- done after vaginal hysterectomy or at time of repair of other pelvic floor defects
 - done before other parts of procedure
- vaginal apex grasped and inverted
- vaginal wall incised and peritoneal sac dissected free from vaginal wall laterally, bladder anteriorly, and rectum posteriorly
- peritoneal sac opened, contents packed into peritoneum, and sac closed at neck with purse-string suture then modified McCall stitch placed

2) abdominal enterocele repair

- ONLY done at time of another abdominal procedure
- approximation of uterosacral ligaments (if uterus removed) + obliteration of cul-de-sac with Moschowitz type or Halban type sutures } be careful of ureters
- doesn't support vaginal vault } need separate colpopexy or vaginal approach

3) vaginal vault prolapse repair

→ recurrent or new anterior vaginal wall prolapse more common

a) sacrospinous ligament fixation

- for total procidentia, post-hysterectomy vault prolapse, post-hysterectomy enterocele
- suture placed 1.5 - 3.0cm medial to ischial spine to avoid injury to pudendal nerves & vessels

→ cure rate of 70-90%

→ historically had high recurrence or new onset of anterior vaginal prolapse (20-90%)

b) uterosacral ligament suspension

- prophylaxis at hysterectomy or for vault prolapse
- sutures through uterosacral ligament are secured to pubocervical & rectovaginal fasciae then McCall suture reapproximates ligaments in midline

→ cure rate 80-90%

→ recurrence rates 10-15% (< sacrospinous fixation)

c) iliococcygeus suspension

- sutures placed bilaterally into fascia of iliococcygeus muscle anterior to ischial spines and then attached to vault

→ cure rates 80-90%

4) abdominal sacral colpopexy

→ after failed vaginal repair, if concomitant abdo Sx req'd, or surgeon preference

→ suspension mesh from vaginal vault to upper sacrum (S1-S2) and promontory

- autologous, allograft, synthetic

- cure rates of 80-100%

→ recurrent or new posterior vaginal wall prolapse more common

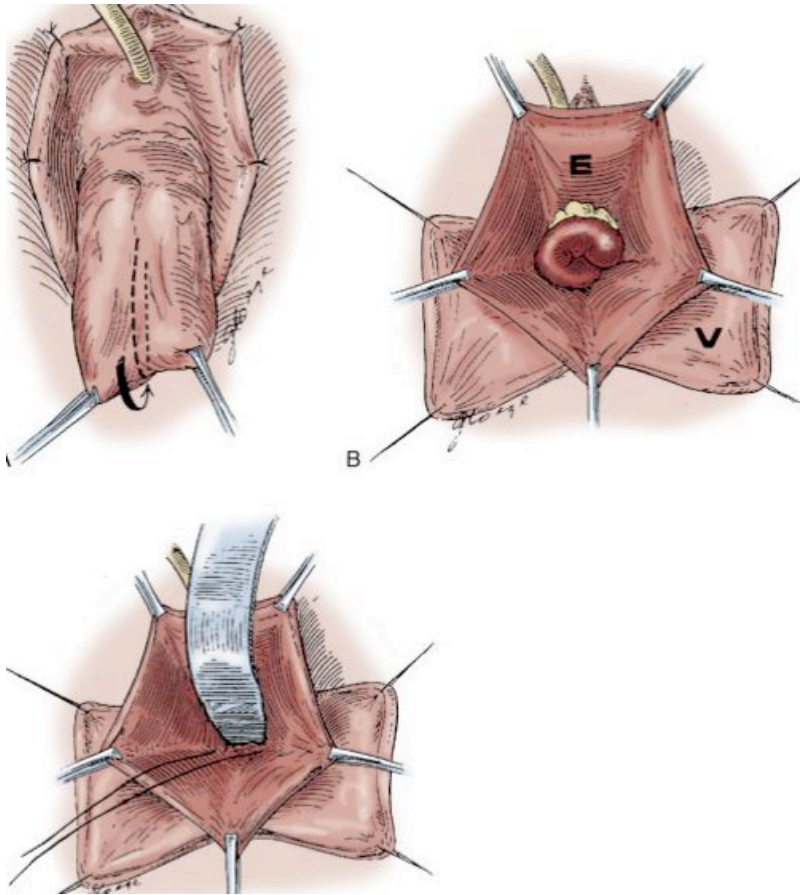
→ **longer OR time, longer time to return to work, more expensive compared to vaginal fixation**

→ **lower recurrence rate and dyspareunia rate than vaginal fixation**

5) laparoscopic prolapse repair

→ mainly uterosacral ligament suspension & sacral colpopexy

→ less blood loss, less post-op pain, shorter stay, longer OR time, similar complication & recurrence rates



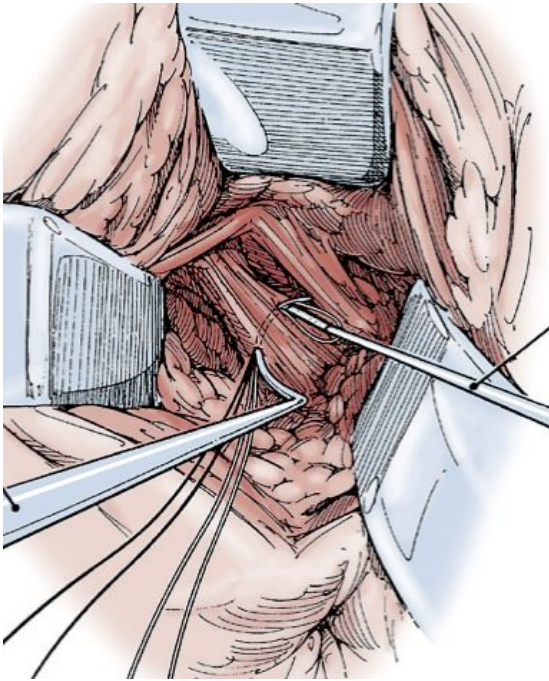
→ VAGINAL ENTEROCELE REPAIR

What are the risks & benefits of the different vaginal vault prolapse apical repairs (CHART)?

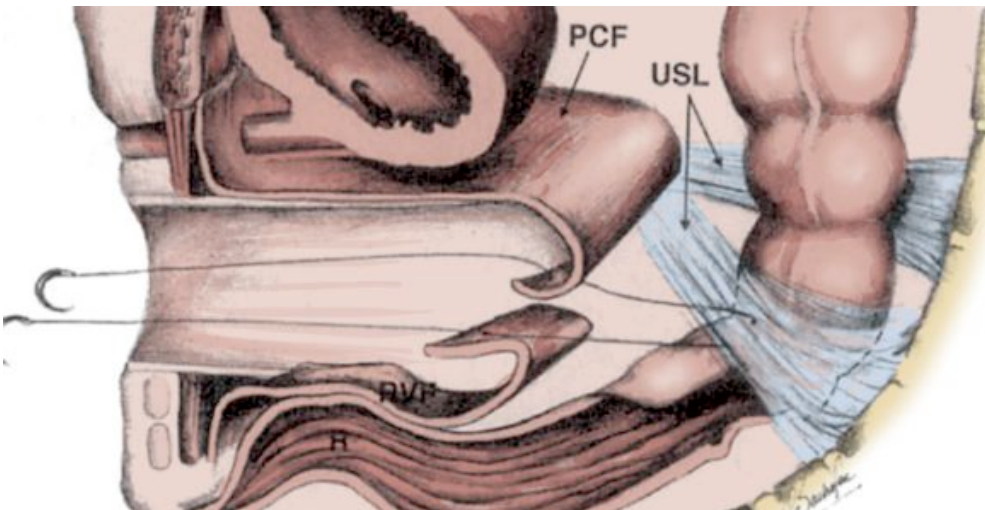
Procedure	Risks	Benefits
Sacrospinous ligament Fixation	<ul style="list-style-type: none"> - post-op anterior prolapse - injury to pudendal & sciatic nerves - injury to pudendal & inferior gluteal vessels - ligament may be atrophied in elderly - technically difficult 	<ul style="list-style-type: none"> - no ureteral injury - rectal injury is rare
Uterosacral ligament Suspension	<ul style="list-style-type: none"> - entry into peritoneum - may be adhesions - possible bowel & ureteral injury - ligaments may not be good 	<ul style="list-style-type: none"> - normal vaginal supports - resultant vaginal axis is physiologic
Iliococcygeus Suspension	<ul style="list-style-type: none"> - possible shortened vagina - least literature 	<ul style="list-style-type: none"> - no vital structures nearby

What are the potential complications of vaginal apical repairs?

- sacrospinous ligament fixation, uterosacral ligament suspension, iliococcygeus suspension
- hemorrhage
- injury to pelvic organs } bladder, urethra, rectum, small bowel, ureters
- rectovaginal fistula
- vaginal adhesions, narrowing
- nerve damage } femoral, peroneal, sciatic
- recurrence



→ SACROSPINOUS LIGAMENT FIXATION

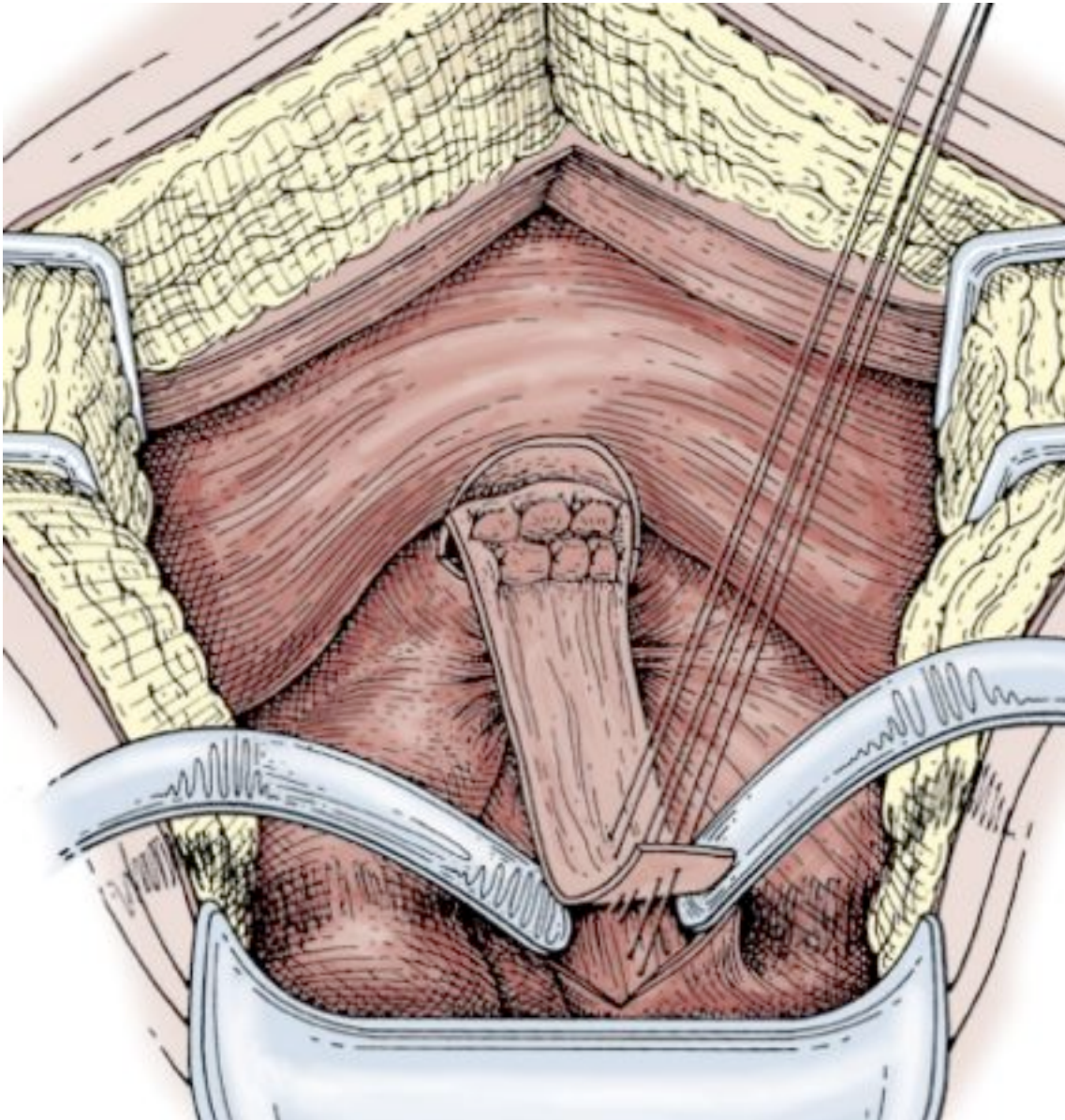


→ UTEROSACRAL LIGAMENT SUSPENSION

What are the potential complications of abdominal apical repairs?

→ sacral colpopexy

- recurrence } rectocele most common
- mesh erosion
- bleeding
- bowel obstruction
- injury to pelvic organs } bladder, rectum, bowel
- vesicovaginal fistula



→ ABDOMINAL SACRAL COLPOPEXY

Posterior Vaginal Wall and Perineum (Posterior Compartment)

What are the 3 causes of rectoceles?

- 1) low rectocele } disruption of distal vaginal supports (vaginal wall, perineal membrane, perineal body)
- 2) midvaginal rectocele } loss of lateral supports or defect in rectovaginal septum
- 3) high rectocele } loss of lateral or apical vaginal supports or defect in rectovaginal septum
- 4) combination

What are the goals of posterior colporrhaphy for rectocele repair?

- 1) plication of prerectal and pararectal fascia in the midline
- 2) narrowing of posterior aspect of levator hiatus by levator plication
- 3) repair of perineal body (perineorrhaphy)

What are the indications to posterior colporrhaphy?

- only recommended for symptomatic patients
 - constipation
 - difficult defecating
 - manual evacuation
 - protrusion
 - dyspareunia
- repair itself is associated with increased dyspareunia and worsening defecatory symptoms

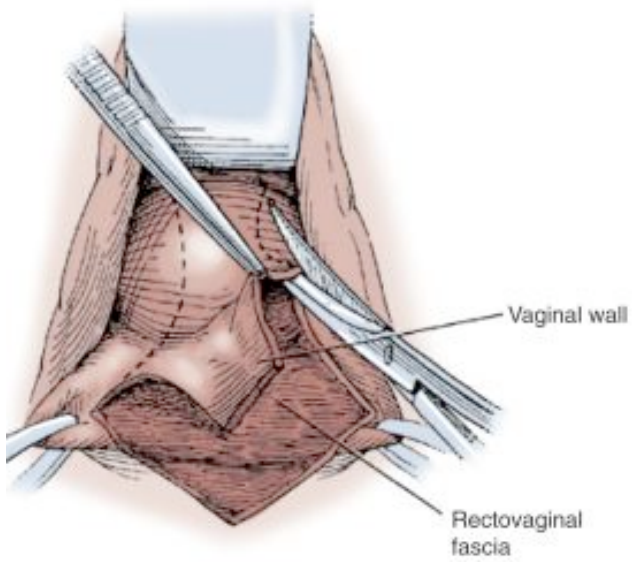
What are the different POSTERIOR compartment procedures for POP?

1) posterior colporrhaphy and perineorrhaphy

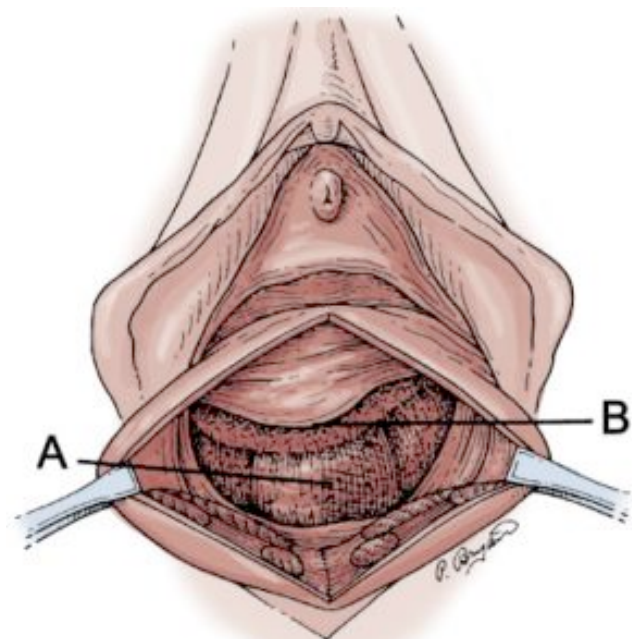
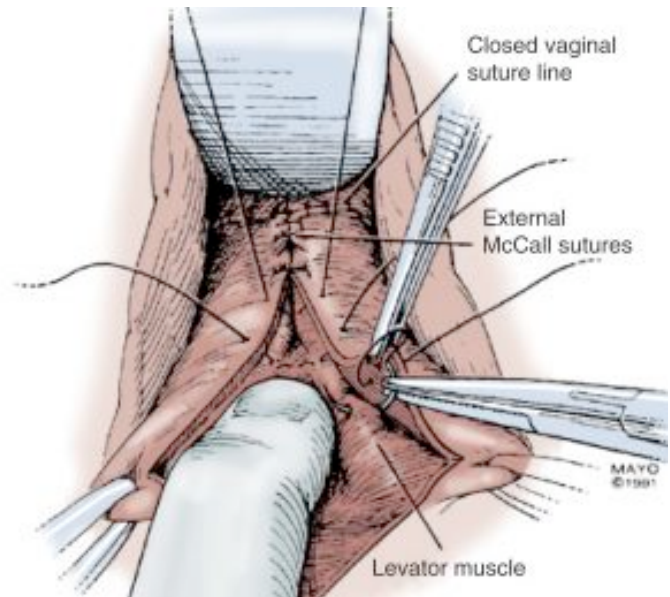
- triangular flap of posterior vaginal wall excised off rectal wall posteriorly
 - avoid excess vaginal narrowing
- exposed rectovaginal fascia and pararectal fascia are brought together in midline along with full-thickness vaginal mucosa
- perineal body reconstructed if there is separation of perineal muscles
 - approximation of superficial and deep perineal muscles toward midline
- elimination of bulge in 75-90%
- recurrence of rectocele in ~15%
- improvement of bowel symptoms in 60-90%
- dyspareunia in 20-50% (excessive tightness of introitus or vagina)

2) rectovaginal fascia defect repair

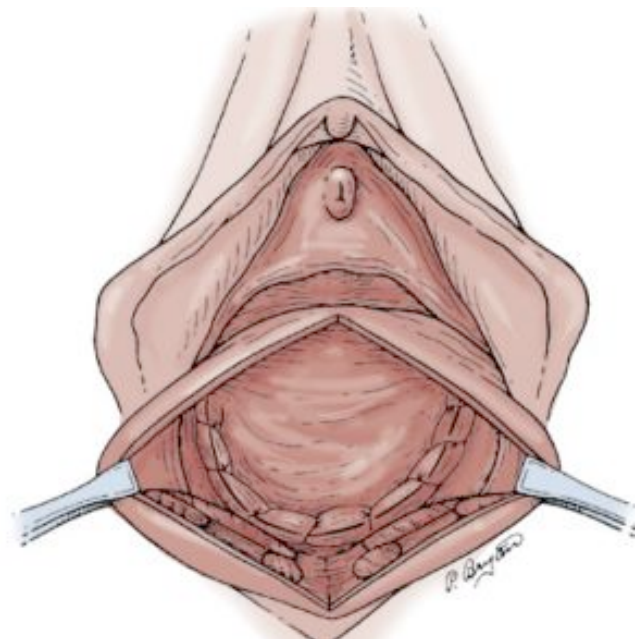
- midline posterior incision w/ lateral dissection of mucosa to expose rectovaginal fascia or septum
- discrete transverse fascial tears sutured together to close defect
- perineal muscles brought together but levator muscles not plicated
- elimination of bulge in 80-90%
- higher recurrence rate of rectocele (30%) cf standard posterior colporrhaphy
- similar rate of post-op bowel complaints and dyspareunia



→ POSTERIOR COLPORRHAPHY



→ RECTOVAGINAL FASCIAL DEFECT REPAIR



Chapter #67 – Pubovaginal Sling

What factors determine the surgical option of choice for SUI?

- 1) underlying condition } degree of urethral mobility, VLPP
- 2) outcome data on various procedures
- 3) surgeon preference & expertise
- 4) patient-factors } age, comorbidities, desire for fast recovery vs complete success, avoidance of complications

What are the surgical options for management of SUI?

- 1) urethral bulking agents
- 2) slings } most efficacious for long-term success
 - } PVS & midurethral
 - autologous fascia best material for PVS (rectus fascia best)
 - midurethral slings (eg TVT, TVT-O, etc) are comparable
- 3) suspensions } transvaginal needle & retropubic (eg MMK or Burch colposuspension)
 - retropubic better but more invasive
- 4) sphincter prostheses } AUS
 - } good results as primary or re-do but higher morbidity
 - } abandoned (especially in women) for faster, easier, less invasive slings
- 5) diversion } last resort option for severe sphincteric damage

→ **newer slings comparable to old gold standard (PVS & retropubic suspension) } 80-95% success**

SPECIFIC INDICATIONS FOR FASCIAL SLINGS

What are the indications for use of autologous PVS for SUI?

- loss of proximal urethral closure function } best option
 - neuropathic conditions } MMC
 - } APR for colon Ca
 - } radical hysterectomy for cervical Ca
 - } post-RP
 - } SCI
 - tissue loss after urethral diverticulectomy
 - erosion of an AUS
 - erosion of a synthetic sling
 - pelvic trauma with fracture
 - urethral erosion from chronic catheterization
 - urethral fistula
- weakness of proximal urethral closure } good option
 - genuine SUI
 - incontinence after failed anti-incontinence surgery

SLING MATERIALS

What are the different materials used for PVS?

- autologous } - rectus fascia - vaginal wall
 - fascia lata - rectus pedicle flap
- cadaveric allografts } - fascia lata
 - acellular dermis
- xenografts } - porcine dermis - porcine small intestinal submucosa (SIS)
 - bovine pericardium
- synthetic material

What are the advantages & disadvantages of the different materials used for PVS?

	ADVANTAGES	DISADVANTAGES
→ AUTOLOGOUS		
rectus fascia	biocompatible	increased OR time to harvest increased post-op pain risk of S/P seromas
fascia lata	biocompatible	increased OR time to harvest increased post-op pain need to reposition patient
→ ALLOGRAFTS		
fascial lata or acellular dermis	shorter OR time less post-op morbidity	1 in 8 million risk of HIV transmission 1 in 3.5 million risk of Creutzfeldt-Jakob prion transmission
→ XENOGRAFTS		
porcine dermis or porcine SIS or bovine pericardium	shorter OR time less post-op morbidity	questionable long-term efficacy risk of zoonotic infections

How is cadaveric allograft and xenograft material processed?

- 1) solvent dehydration \ remove genetic material and prevent
- 2) lyophilization (freeze-dry) / transmission of infection
- 3) gamma irradiation } secondary sterilization

EVALUATION OF PATIENTS FOR SLINGS

What is involved in the work-up prior to PVS for urinary incontinence?

- 1) provocative tests to help confirm Dx
 - sitting & standing Valsalva stress tests
 - Marshall test
 - Q-tip test
 - 2) pelvic exam to r/o concomitant prolapse or urethral diverticulum
 - 3) +/- UDS to r/o low compliance bladder & assess VLPP
 - low compliance must be treated before addressing urethral dysfunction
 - VLPP helps characterize degree of urethral dysfunction but not very clinically predictive
 - 4) minimal role for UDS to r/o detrusor overactivity
 - surgical correction of SUI improves/cures urge incontinence in 60-80%
 - ~10% will develop de novo urge incontinence after surgical correction of SUI
- no indication to do urethral pressure profile } low pressure urethra DOES NOT predict higher failure
and does not correlate well with VLPP

OPERATIVE PROCEDURE

- sling should be located **at level of proximal urethra** } both ends should be in retropubic space
- if poor urethral function + minimal hypermobility in neurogenic condition, crossover sling technique can be used to achieve circumferential compression

MODIFICATIONS OF THE STANDARD SLING

POST-OPERATIVE CARE

What are the important aspects of the post-op care after PVS for incontinence?

- vaginal packing out POD#1
- early ambulation to prevent DVT
- avoid strenuous activity for 4-6 wks
- no sexual intercourse for 3-4 wks
- TOV on POD#1
 - if intra-op cystotomy occurred, Foley x 1wk, then removal after N cystogram
- CIC if high PVRs
 - temporary catheter if unable to do CIC for 1 wk

COMPLICATIONS AND PROBLEMS

What are the potential complications of PVS for incontinence?

- peri-op
 - bleeding
 - cystotomy
 - urethral injury
 - button hole vaginal mucosa
 - bowel injury (rare)
- early post-op
 - retention } early urethrolysis (<6wks) if high index of suspicion for obstruction
 - if late & urethra is hypersuspended, likely need to completely remove sling under urethra & takedown lateral attachments
 - bleeding
 - wound infection
 - UTI
 - **de novo urge symptoms** } **occurs in ~10%**
 - sling failure } not enough tension
 - erosion (rare) } usually due to traumatic catheterization
 - } Foley x 10days
 - S/P pain } usually goes away in 2-3 wks once sutures dissolve
- late post-op
 - erosion (rare) } incise sling and close urethra
 - retention
 - sling failure } usually due to vaginal prolapse that pulls on sling
 - osteitis pubis

OUTCOMES STUDIES

How successful are autologous rectal fascia PVS for incontinence?

- ~70-95% cure rate at 4-5yrs \
- very high QOL scores /
- less successful with autologous fascia lata (~60%)
- cadaveric slings much worse (50%)
- little data available for xenograft slings
- ~80% cure rate when combined with prolapse repair
- good results for autologous PVS at same time as urethral reconstruction, urethral diverticulectomy
 - cure rates of ~90%

Chapter #68 – Tension-Free Vaginal Tape

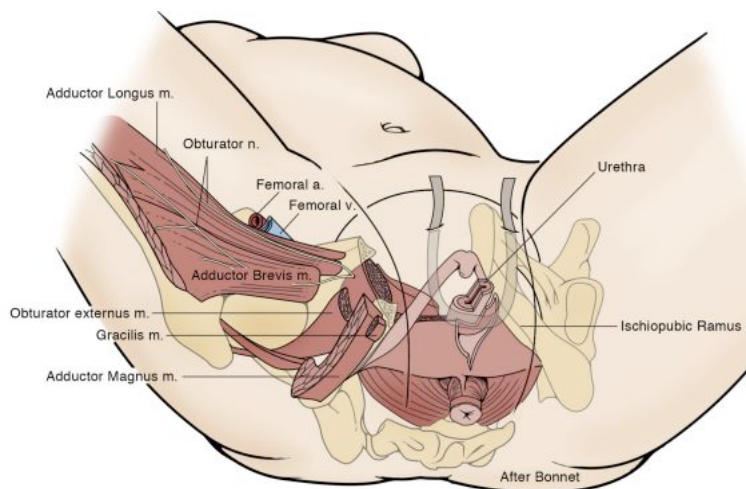
THE TENSION-FREE VAGINAL TAPE PROCEDURE

What is the “midurethral theory” of stress incontinence?

- Petros & Ulmsten } aka integral theory
- injury from surgery, parturition, aging, or hormonal deprivation leads to weakening or damage of pubourethral ligaments, impairing midurethral function and anterior urethral wall support
- not just ligamentous injury but also weakening of pubococcygeal muscles at level of midurethra

List the different types of TVT slings.

- vaginal approach (bottom-up)
 - TVT
- abdominal approach (top-down)
 - SPARC



→ MIDURETHRAL SLINGS } TVT

What are the potential complications of TVT surgery for incontinence?

- peri-op
 - bladder perforation (2-4%)
 - urethral injury
 - bleeding
 - wound infection
 - UTI
 - bowel perforation (rare)
 - vascular injury (rare)
- post-op
 - retention (1-10%) } consider sling release at ~4wks (continence usually maintained in most)
 - **de novo urge symptoms (5-10%)** } more common with older age – up to 40%)
 - persistent incontinence } mainly from misplacement of tape or inadequate tension on tape
 - urethral erosion

What are the management options for TVT erosion?

- 1) vaginal erosion
 - presents with vaginal D/C, palpable rough surface, pelvic pain, dyspareunia (patient & partner), LUTs, inguinal discomfort
 - a) **observation } for select patients with asymptomatic & small caliber erosions**
 - +/- estrogen cream
 - b) vaginal advancement flaps
 - c) excision } for failure of conservative therapy
- 2) urethral erosion
 - presents with LUTs (urgency, urgency incontinence, retention, etc), recurrent UTIs, persistent incontinence, hx of CIC
 - **observation is CONTRAINDICATED**
 - a) transvaginal excision of tape + closure of urethrotomy
 - +/- Martius fat pad for coverage
 - may place autologous PVS at time of surgery
 - b) endoscopic tape transection (newer option)
- 3) bladder erosion
 - likely unrecognized intra-op perforation & placement of TVT in bladder
 - presents with lower abdo pain, intermittent gross hematuria, recurrent UTIs, LUTs (urgency, frequency, dysuria, etc), persistent incontinence
 - **observation is CONTRAINDICATED**
 - a) combined transvaginal + retropubic approach
 - b) endoscopic excision

How successful are TVTs for incontinence?

- 80-90% success rate
- cures 60-80% of concomitant urge incontinence, urge symptoms
- good success rates even for mixed incontinence

What are the RFs that predict poor outcomes with TVTs?

- older age } de novo urge symptoms more common, lower QOL scores
- presence of ISD
- obesity } controversial
 - } infections more common
- concomitant pelvic organ prolapse repair } transient retention more common
 - } comparable success rates
- previous urethral surgery/re-do surgery } risk of bladder perforation slightly higher
 - } success rates lower
- local RADs

What are the RFs for urethral erosion of a TVT? } } } “Dissect CUTTER ”

- **Dissection** too close to urethra (devascularization)
- **Catheterization/dilation** (traumatic)
- **Urethral injury** at time of insertion (iatrogenic)
- **Tension** (excessive)
- **Twisting** of tape
- **Estrogen deficiency** (eg older age)
- **Radiation**

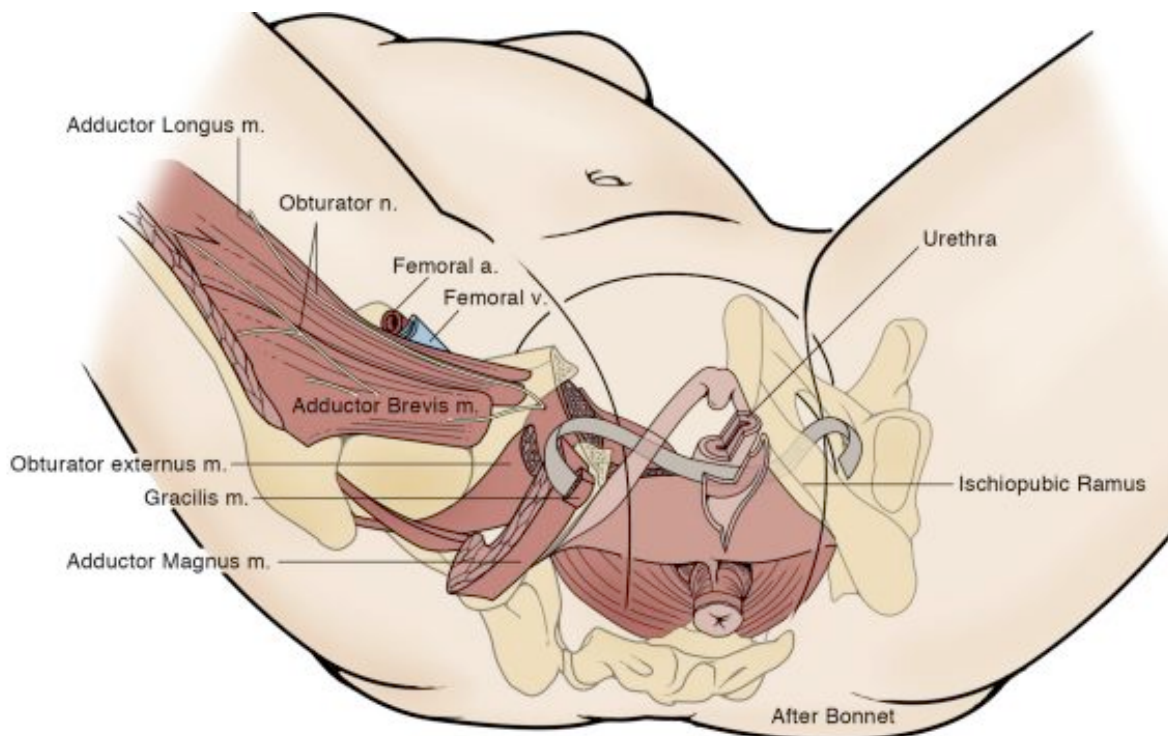
TRANSOBTURATOR SLINGS

List some of the muscles that are traversed by the implanted sling during TOT insertion for incontinence?

- should never penetrate adductor longus muscle } safe distance away from neurovascular structures
- should never penetrate levator ani muscles
- adductor magnus
- adductor brevis
- gracilis
- obturator externus
- obturator internus

What nerves are close to the path of the material used in TOT?

- obturator nerve
- dorsal nerve of clitoris
- pudendal nerve



→ MIDURETHRAL SLINGS } TOT

What are the different types of TOT slings?

- through obturator foramen instead of up through retropubic space as in TVT
- 1) Outside to In } ObTape, Monarc, UraTape, BioArc
- 2) Inside to Out } TVT-O

How successful are TOT slings for incontinence?

- similar to TVT } 80-90% success rate
- } cures 60-80% of concomitant urge incontinence, urge symptoms
- } good success rates even for mixed incontinence
- trend toward less bladder injuries & less bleeding } maybe less voiding dysfunction

What are the potential complications of TOT surgery for incontinence?

→ peri-op

- **post-op leg pain (10-15%)** } usually transient (worse with inside-out)
- bladder perforation (rare) } no cases with inside-to-out (TVT-O) approach
- vaginal perforation (more common than retropubic approaches)
- urethral injury
- bleeding
- wound infection, thigh abscess
- UTI
- vascular injury (rare)

→ post-op

- retention (1-10%) } consider sling release at ~4wks (continence usually maintained in most)
- de novo urge symptoms (~5%)
- persistent incontinence } mainly from misplacement of tape or inadequate tension on tape
- urethral erosion

List the main advantages & disadvantages of TVT-O (inside-out) over the TOT (outside-in) approach.

→ advantages of TVT-O

- smaller vaginal incision
- lower bladder perforation rate
- ?less bleeding risk

→ disadvantages of TVT-O

- more leg pain

Chapter #69 – Injection Therapy for Urinary Incontinence

PATIENT SELECTION

What are the characteristics of an ideal injectable agent?

- biocompatible
- causes little inflammatory or FB reaction
- does not migrate
- uniformity in size
- maintains bulking effect long term
- easily injected
- should adhere well to tissues

What are the goals of injectables for incontinence?

- correct SUI that occurs with increased Pabd } not to increase resistance to Pdet
- to restore mucosal coaptation

What are the indications for injection therapy for incontinence?

- ISD + N bladder capacity and compliance + good anatomic support } **not ideal if significant hypermobility component**
- high risk for major surgery
- patient preference
- previous surgical failure

What are the contraindications to injection therapy for incontinence?

- active UTI
- untreated detrusor overactivity
- known hypersensitivity/allergy to proposed agent

What is involved in the pre-op evaluation prior to injection therapy for incontinence?

→ UDS to r/o bladder causes of incontinence (eg OAB)

→ males

- r/o BN contractures
- must be injected proximal to EUS } hx of RADs may decrease success

→ females

- if combined ISD + significant hypermobility, may do better with alternative options
- must be injected at BN and proximal urethra

→ kids

- if patulous BN that is fixed open, likely will do better with alternative option (eg AUS)

INJECTABLE MATERIALS

List the different injectable agents used for incontinence.

→ organic materials

- 1) PTFE } risk of migration
- 2) glutaraldehyde cross-linked } mainly type I collagen
 bovine dermal collagen } completely degrades by 19 mos but residual connective tissue persists
 (GAX-collagen) } must do allergy testing

→ synthetic materials

- 1) durasphere
- 2) ethylene vinyl alcohol (EVOH) in DMSO
- 3) Macropastique (silicone in povidone) } concerns with migration
- 4) Zuidex (dextranamer & hyaluronic acid)

→ autologous material

- 1) blood
- 2) fat (risk of embolism)
- 3) cartilage (ear)

INTRAURETHRAL INJECTION TECHNIQUES

What are the different techniques used to inject various agents for incontinence?

→ goal is to inject in wall of urethra

→ want to see coaptation of urethra (except with EVOH)

- 1) transurethral } men & women
- 2) periurethral } women
 - less bleeding & extravasation of agent
 - higher rate of retention & more volume of material needed
- 3) per rectum
- 4) per vagina
- 5) suprapubic antegrade } men

POST-OP CARE

What are the important post-op management points following injectable therapy for incontinence?

- peri-op ABx for 2-3 days
- CIC with small (10-14Fr) catheter if retention } avoid indwelling catheters

EFFICACY OF INJECTABLE TREATMENT

What are the 3 main disadvantages of injectable therapy for incontinence?

- 1) don't know how much to use for each patient
- 2) safety of non-autologous agents } migration, FB reaction, immunologic effects
- 3) lack of durability

How successful is injection therapy for incontinence?

- 70-80% success rate } short term only
 - poor long term results

COMPLICATIONS

What are the potential complications of injectable therapy for incontinence?

- peri-op (uncommon)
 - urethral bleeding
 - bladder perforation (rare & minor)
 - extravasation of agent
 - allergic reaction to material (collagen)
- post-op
 - retention (~20%) } transient in most
 - LUTs/storage symptoms (~20%) } transient in most
 - **de novo urgency, urgency incontinence (10-50%)**
 - UTI
 - persistent incontinence
 - sterile abscess, granuloma
 - PE (autologous fat)
 - migration of material (eg PTFE)
 - epididymitis
 - balanitis
 - pain at injection site

SAFETY

What are the safety issues with the different injectable agents used for injectable therapy?

- PTFE } risk of migration
 - ?carcinogenic risk of FB granuloma that forms after particle migration
- GAX-collagen } risk of allergic reaction
 - skin test prior to injection
- autologous fat } fat embolism

PRESENT AND FUTURE OF INJECTABLES IN URINARY INCONTINENCE

What other injectable agents have been described for incontinence?

- Hyaluronic acid + dextranomer microspheres (Zuidex)
- Hylagel (hyaluronic acid)
- Bioglass (Ca oxide, Ca silicone, Na oxide mixture)
- Ca Hydroxyapatite
- autologous chondrocytes
- injectable balloons (ProACT)

[illegible]

- **Breastfeeding**
- **Lou Gherig disease (ALS)**
- **Aminoglycoside use**
- **Myasthenia gravis**
- **Eaton-Lambert syndrome**
- **Pregnancy**

Chapter #71 – Geriatric Incontinence & Voiding Dysfunction

THE IMPACT OF AGE ON INCONTINENCE

How common is urinary incontinence in the elderly?

- 15-30% of elderly living at home
- 33% of elderly in acute care setting
- 50% of elderly in NH

List conditions that elderly patients with urinary incontinence are predisposed to.

- perineal rashes
- pressure ulcers
- UTIs
- urosepsis
- falls
- fractures

List changes in the elderly that predispose them to urinary incontinence?

→ incontinence is NOT A NORMAL FINDING OF AGING

→ anatomic changes

- ↓'d bladder sensation
- ↓'d bladder contractility
- ↓'d ability to postpone voiding
- shortening of urethra in F
- atrophy of striated EUS in F

→ physiologic changes

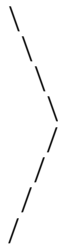
- ↑'d prevalence of involuntary bladder contractions
- ↑'d volume of diuresis at night
- polypharmacy
- comorbidities more common (eg DM, CHF, etc)

CAUSES OF TRANSIENT INCONTINENCE

List the causes of transient urinary incontinence (CHART).

→ “DIAPPERS”

- **D**elirium
- **I**nfection (symptomatic UTI)
- **A**trophic vaginitis/urethritis
- **P**sychological (depression, neurosis)
- **P**harmacologic (meds)
- **E**xcess urine production
- **R**estricted mobility
- **S**tool impaction



seen especially in
the elderly

List medications that can cause transient incontinence (CHART).

- | | |
|---|---|
| - sedatives-hypnotics (eg diazepam) | → sedation, delirium |
| - EtOH | → polyuria, frequency, urgency |
| - anticholinergics (eg diphenhydramine) | → retention, overflow |
| - anti-psychotics (eg haldol) | → sedation, retention |
| - anti-depressants (eg amitriptyline) | → sedation, retention |
| - anti-parkinsonians (L-dopa) | → sedation, retention |
| - narcotics | → retention, delirium |
| - α -blockers (eg terazosin) | → SUI in F |
| - α -agonists (eg nasal decongestants) | → retention in M |
| - CCBs | → retention |
| - potent diuretics | → polyuria, frequency, urgency |
| - NSAIDs | → nocturnal diuresis from fluid retention |
| - ACE inhibitors | → cough-related SUI in F |
| - vincristine | → retention from neuropathy |

ESTABLISHED INCONTINENCE

List non-transient causes of urinary incontinence in the elderly.

- 1) **OAB (most common lower urinary tract cause)** } anatomic changes at cellular level alter bladder smooth muscle activity
→ “complete dysjunction pattern”
- 2) SUI
- 3) BOO } more common in M
} overflow incontinence
- 4) detrusor underactivity } uncommon
} overflow incontinence
- 5) functional incontinence

What is the most common form of detrusor overactivity in the elderly.

- can have OAB with preserved contractile function OR impaired contractile function
- **OAB w/ impaired contractility is most common** } **“detrusor hyperactivity w/ impaired contractility”**
→ **DHIC**
 - coexistence of detrusor overactivity + cystopathy
 - can lead to retention } mimics BOO
 - can seem like SUI } weak contractions induced by valsalva may not be detected
 - standard anti-cholinergic Rx for storage symptoms can easily induce retention

DIAGNOSTIC APPROACH

What is involved in the initial w/u of incontinence in the elderly?

- 1) History } characterize any incontinence
 - frequency, severity, type, degree of bother, effect on QOL, precipitants, previous treatment to date, pad use, etc
 - } **need to assess lower GU tract, bowel fxn, sexual fxn, & local symptoms**
 - LUTS } frequency, urgency, nocturia, weak stream, intermittency, straining, incomplete emptying
 - } hx of UTIs, AUR, hematuria, etc
 - anal incontinence, difficulty defecating/constipation
 - dyspareunia, decreased desire (most common)
 - local symptoms include vaginal pressure/heaviness, vaginal/perineal pain, low back pain, abdo pressure or pain, palpable bulge/mass
 - } **voiding diary (3 days optimal), fluid intake habits, pad tests, questionnaires**
 - } ask about RFs for incontinence + r/o causes of transient incontinence
 - vaginal deliveries, obese, poor nutrition, smoker, activity level, etc
 - **DIAPPERS**
 - } PMHx (eg stroke, MS, SCI, RADs, menses, etc)
 - } PSHx (APR, hysterectomy, RP, etc)
 - } meds, allergies, drugs
- 2) P/E } neurologic exam (gait, perineal sensation, bulbocavernosus reflex, cognitive status)
 - } abdo exam (distended bladder, masses, hernias, DRE, etc)
 - } female pelvic exam (vaginal atrophy, skin excoriation, vault exam, organ prolapse, pelvic floor muscle strength, cough test, Q-tip test, Marshall test, +/- dye tests)
 - **need to r/o prolapse associated w/ occult or masked SUI**
 - lithotomy and standing exams
 - if incontinence not demonstrable in lithotomy, repeat in standing position
 - Q-tip test = urethral hypermobility
 - Marshall test = anterior vaginal wall
 - **anterior, apical/middle, and posterior compartment**
 - also assess rectovaginal septum, perineal body, anal sphincter, pelvic floor muscles
- 3) routine lab tests } urinalysis, urine C&S, +/- cytology +/- serum creatinine
- 4) initial investigations } uroflow + PVR
- 5) (WHEN INDICATED) additional testing } cystoscopy + UDS + imaging + EMG
 - CMG } detrusor overactivity, low compliance, VLPP, DLPP
 - PFS } high pressure + low flow, low pressure + low flow
 - } BOOI >40 is obstruction [$P_{det}Q_{max} - 2(Q_{max})$]
 - } BCI <100 is poor contractility [$P_{det}Q_{max} + 5(Q_{max})$]

List causes of nocturia (CHART).

- volume related
 - age-related diuresis
 - excess intake/EtOH
 - caffeine, diuretics, theophylline, lithium
 - endocrine/metabolic } DM, DI, hyperCa
 - peripheral edema } CHF, low albumin states, PVD, venous insufficiency, NSAIDs
- sleep related
 - insomnia
 - obstructive sleep apnea
 - pain
 - dyspnea
 - depression
 - drugs
- lower urinary tract related
 - small capacity
 - detrusor overactivity
 - decreased compliance
 - prostate related/overflow incontinence
 - sensory urgency

THERAPY

What are the recommended treatment options for urinary incontinence in the elderly (CHART)?

- **r/o transient causes } DIAPPERS**
- **r/o functional incontinence**
- OAB + N contractility
 - 1) bladder retraining or timed voiding
 - 2) meds to relax bladder if indicated & no contraindications
 - 3) indwelling catheter not recommended (can induce more spasms)
 - 4) can try inducing retention pharmacologically and start CIC or indwelling
- DHIC
 - 1) bladder retraining or timed voiding (if not in retention) +/- meds to relax bladder (low doses)
 - even low doses of anti-muscarinics can induce retention
 - 2) if high PVR (>150cc) then consider double voiding, Crede, or CIC +/- bladder relaxant meds
 - 3) indwelling catheter if neither option above feasible
- SUI
 - 1) conservative measures } wt loss, treatment of cough, pessary
 - 2) if leakage at certain volumes, adjust fluid excretion and timed voiding
 - 3) pelvic muscle exercises +/- biofeedback or weighted intravaginal cones
 - 4) imipramine or α -agonist +/- estrogen if not contraindicated
 - 5) surgery
- urethral obstruction
 - 1) conservative measures } adjust fluid excretion, timed voiding
 - r/o hydro, elevated PVR, recurrent UTIs, gross hematuria
 - 2) α -blockers and bladder relaxants (if coexistent OAB)
 - 3) finasteride
 - 4) surgery } TURP
- underactive detrusor
 - 1) if unknown duration, decompress for several wks then perform TOV
 - 2) Crede, double voiding, etc +/- α -blockers
 - bethanecol rarely useful
 - 3) CIC or indwelling catheter

List some bladder relaxant medications used for urgency incontinence (CHART).

- 1) anti-cholinergics } eg oxybutynin, tolterodine, darifenacin, solifenacin, trospium
 - 1st line drugs of choice
 - dose adjust trospium in renal insufficiency
- 2) TCAs } eg imipramine
 - 2nd line therapy
 - may be helpful for women w/ mixed incontinence (coexistent SUI)
- 3) smooth muscle relaxants } eg flavoxate
 - not proven effective in placebo-controlled trials
- 4) CCBs } diltiazem
 - no positive controlled trial

What are the principles of a TOV after placement of an indwelling urethral catheter (CHART)?

- 1) ensure bladder has been decompressed for several days at least (7-21 days if possible)
 - the higher the PVR, the longer the bladder should be decompressed
- 2) correct reversible causes of AUR (eg constipation, pelvic pain, anti-cholinergic use, etc)
- 3) treat delirium, depression, atrophic vaginitis, UTI, etc
- 4) α -blocker has benefit in men, but is unproven in women
 - initiate several days prior to TOV
 - also consider 5ARI in men
- 5) record baseline urine output for 2 days prior to TOV
- 6) remove catheter in AM to allow accurate measurement of urine output & facilitate re-catheterization if necessary
- 7) reinsert catheter ONLY
 - a) after patient voids to determine PVR
 - b) after expected bladder volume exceeds preset limit (eg 600-800cc)
 - c) if patient in painful retention
- 8) if patient voids and PVR is
 - >400cc, reinsert catheter and evaluate further
 - 100-400cc, watch for delayed retention and evaluate further
 - <100cc, watch for delayed retention
- 9) if unable to void, evaluate further if appropriate, otherwise start CIC or permanent indwelling catheter

What are the principles of indwelling catheter care (CHART)?

- 1) maintain sterile, closed gravity drainage system
 - secure catheter to upper leg or abdomen to avoid irritation and contamination
 - empty bag q8hrs
 - do not routinely irrigate catheter
 - do not clamp or kink drainage tubing & keep bag below level of bladder at all times
 - avoid frequent cleaning of urethral meatus; soap + water OD is sufficient
 - adding disinfectants to catheter bag is ineffective
- 2) "bypassing" is likely bladder spasms & can be treated by minimizing balloon size +/- anticholinergics
- 3) **do not treat asymptomatic bacteriuria & do not use ABx prophylaxis**
- 4) **surveillance cultures unnecessary & can be misleading**
- 5) if symptomatic UTI develops, remove catheter first, then obtain culture
 - until cultures return, ABx coverage should include common uropathogens as well as uncommon ones (eg *Providencia stuartii*, *Morganella morganii*)
- 6) if frequent blockage occurs and cultures reveal *Providencia* or *Proteus*, Abx treatment even in asymptomatic patients may reduce blockage (but can increase resistance)
 - if no urea-splitting bugs, consider acidification if urine output normal
 - if frequent blockage persists, consider using silicone catheter
- 7) catheter should be changed every 1-2 months, although could probably wait longer, especially if catheterization is difficult
 - if obstruction is frequent, change catheter more frequently

Chapter #72 – Urinary Tract Fistula

GENERAL CONSIDERATIONS

What is the definition of a fistula?

- abnormal communication between 2 epithelial- or mesothelium-lined surfaces

What are the causes of fistulae?

- iatrogenic (most common)
- malignancy
- RADs
- parturition
- ischemia
- congenital anomalies
- inflammation & infection

What are the principles of urinary tract fistula management (CHART)?

- adequate nutrition
- elimination of infection
- unobstructed urinary tract drainage or stenting
- removal or bypass of distal urinary tract obstruction
- beware of malignant etiology of fistula

What are the causes of persistent fistulae? } } } **“FRIENDO”**

- **F**oreign body
- **R**adiation
- **I**nfection/ischemia
- **E**pithelialization
- **N**eoplasm
- **D**istal **O**bstruction

What are the principles of surgical repair of urinary tract fistulae (CHART)?

- 1) adequate exposure of fistula tract with debridement of devitalized and ischemic tissue
 - 2) removal of involved FBs or synthetic materials from region of fistula (if applicable)
 - 3) careful dissection or anatomic separation of involved organ cavities
 - 4) watertight closure
 - 5) use of well-vascularized, healthy tissue flaps for repair (atraumatic handling of tissue)
 - 6) multi-layer closure
 - 7) tension-free, non-overlapping suture lines
 - 8) adequate urinary tract drainage or stenting after repair
 - 9) treatment & prevention of infection
 - 10) maintenance of hemostasis
- **fistula tract DOES NOT have to be excised in ALL cases**
→ **urethral + S/P catheter likely best drainage strategy**

UROGYNECOLOGIC FISTULA

→ includes AUA Update #6 – 2006

VVF

What are the causes of VVF (CHART)?

- industrialized world } **iatrogenic (>75%)**
 - hysterectomy (abdominal, vaginal)
 - anti-incontinence surgery
 - anterior vaginal wall prolapse surgery (eg colporrhaphy)
 - vaginal biopsy, vaginal laser procedures
 - other pelvic surgery (vascular, rectal)
- developing world } prolonged obstructed labour due to pressure necrosis (95%)
 - these fistulae tend to be larger, more distal, & harder to fix
- other causes }
 - } pelvic RADs (external beam or brachy)
 - } malignancies (eg cervical, vaginal, and endometrial)
 - } infectious/inflammatory diseases (endometriosis, IBD, TB, etc)
 - } FBs (eg pessary)
 - } external trauma (eg pelvic fracture, sexual trauma)
 - } obstetrical (eg forceps laceration, uterine rupture, C-section injury to bladder)
 - } congenital VVF (commonly associated with other GU abN'ities)

What is the most common procedure leading to VVF?

- **abdominal hysterectomy**
 - bladder injuries are 3x more common with abdominal hysterectomy cf Vag. Hyst.
 - risk of bladder injury during abdominal hysterectomy is ~1%
 - risk of VVF after hysterectomy is ~0.1%
 - usually due to unrecognized cystotomy **near vaginal cuff** or due to tissue necrosis from cautery or suture placement

What is the “obstructed labour injury complex”?

- varying degrees of urethral loss
- VVF
- SUI
- hydroureteronephrosis
- renal failure
- rectovaginal fistulae
- rectal atresia
- anal sphincter incompetence
- cervical destruction
- amenorrhea
- PID
- secondary infertility
- vaginal stenosis
- osteitis pubis
- foot drop

How common are VVFs after pelvic RADs?

- varies with type, dose, and location of RADs } can occur several decades later
- 1.5% incidence after radiation for cervical Ca
- **must r/o recurrence of malignancy** } always consider Bx before definitive repair

What are the RF's for VVF after TAH?

→ general (“DIAPeRS”)

- DM
- Ischemia
- Atherosclerosis
- PID/infection
- RADs
- Steroid use

→ specific (“Make New Cunt PEE”)

- Malignancy
- Neurogenic bladder
- C-section (uterine surgery)
- Pessary use
- Endometriosis
- Endocervical conization (scarring)

What are the 5 factors in preventing VVF during gynecologic surgery?

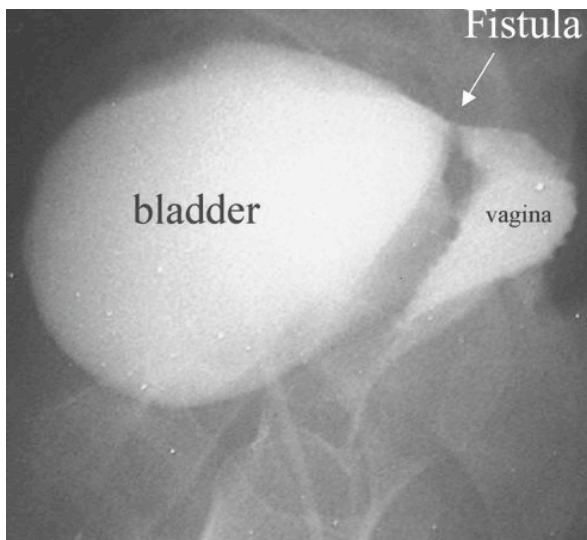
- 1) immediate detection of bladder injury with use of dyes, if necessary
- 2) watertight closure of bladder
- 3) satisfactory extravesical drain placement
- 4) avoidance of vaginal incision, if possible, after recognition of bladder injury
- 5) prolonged, uninterrupted post-op bladder drainage

How do VVFs commonly present?

- **constant urine per vagina (most common)**
- recurrent cystitis
- perineal skin irritation
- vaginal fungal infections
- pelvic pain (rare) } pain uncommon in VVF, unless hx of RADs or skin irritation

What is the DDx of clear vaginal discharge after TAH? }}} “SLUTS Pee”

- Seroma
- Lymph
- Urine } ureterovaginal fistula, VVF, UVF, vesicouterine fistula, urinary incontinence
- Tube (Fallopian) fluid
- Spontaneous vaginal secretions
- Peritoneal fluid



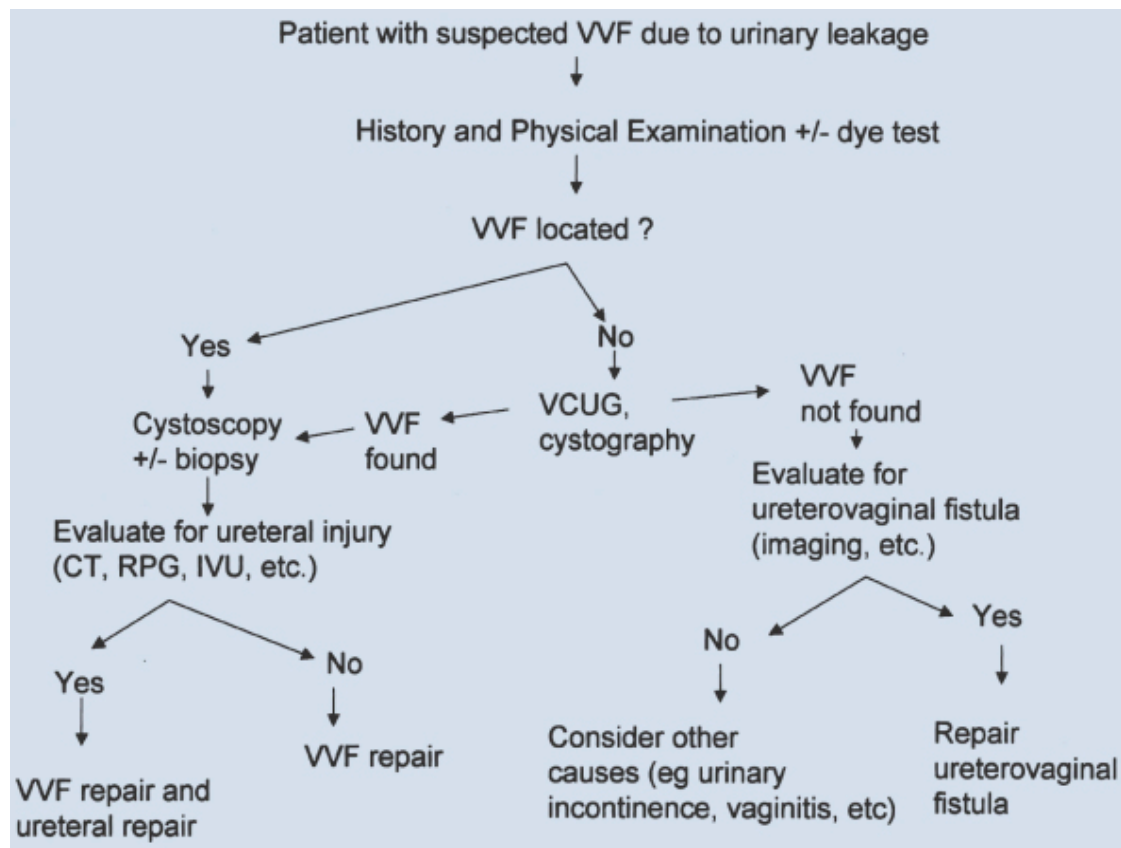
→ CYSTOGRAM OF VVF (lateral image)



→ CT SCAN OF VVF

What is the work-up for a potential VVF?

- 1) History } distinguish from SUI, urgency incontinence, overflow incontinence
 } assess for RFs of VVF ("DIAPRS, Make New Cunt PEE")
 → DM, Ischemia, Atherosclerosis, PID, RADs, steroids, malignancy, neurogenic bladder, C/S, pessary, endometriosis
- 2) P/E } speculum exam to assess fistula +/- vaginoscopy
 } bimanual exam to assess surrounding inflammation and timing of repair
 } look for evidence of postmenopausal atrophy (may need estrogen)
 } look for possible flaps (previous perineum, lower abdomen, thigh surgery)
- 3) lab tests } CBC, serum creatinine, fluid for creatinine, urinalysis, urine C&S
- 4) dye tests } visualize vagina after instillation of blue dye into bladder
 } double dye or tampon test may be indicated (oral Pyridium + blue dye in bladder)
 → to r/o ureterovaginal or urethrovaginal fistula
 - yellow at top of tampon = ureterovaginal fistula
 - blue in middle of tampon = VVF
 - blue at bottom of tampon = urethrovaginal fistula or incontinence
- 5) cystoscopy } helps locate and characterize fistula
 → VVF near U/O may require abdominal approach + reimplant
 } +/- **Bx to r/o malignancy (especially if hx of pelvic malignancy)**
- 6) imaging } cystogram +/- VCUG
 → lateral position is best (vagina and bladder not overlapping)
 } IVP +/- retrograde pyelogram
 → **~10% of post-op VVFs have assoc'd ureteral injury or ureterovaginal fistula**
 } can also utilize CT or MRI



How would you approach the management of a VVF?

→ **goal is rapid cessation of urine leakage } physical & psychological impact**

1) conservative treatment

→ if uncomplicated, small (3mm), oblique VVF + resolution of leakage w/ initial catheter

a) trial of catheter + ABx + anticholinergics for 2-3 weeks

b) coagulation of tract +/- fibrin sealant + catheterization for 2-3 weeks

2) surgical treatment (best chance is first chance)

→ if large uncomplicated VVF OR complicated VVF

- timing

→ 3-6 months delay with obstructed labour

→ ~6 months post-RADs

\ **immediate repair recommended**
/
for uncomplicated VVF
post-gyne Sx

- abdominal vs vaginal approach

→ must consider size, location, need for other procedures and surgeon experience

→ transabdominal may be preferred if augment or reimplant needed

- preferred approach is mainly based on surgeon

→ **most are amenable to transvaginal repair**

- success rate for simple VVF repair is >90%, regardless of abdominal or vaginal

→ success rate decreases with complex VVF

→ **consider interposition flaps/grafts for complex or re-do VVF repairs**

- failed VVF repairs or non-surgical candidates have other options

→ ileal conduit, ureteral occlusion + permanent NTs, ureterosigmoidostomy

What is considered a complicated VVF?

- >3cm in diameter
- recurrent VVF
- prior RADs
- associated with malignancy
- fistula at trigone, BN, or urethra
- compromised area due to poor healing

List methods used to maximize VVF repair outcomes.

- wait until tract mature (immediate repair if uncomplicated post-gyne Sx VVF)
- completely mobilize fistula
- multiple layer closure
- non-overlapping suture lines
- absorbable sutures
- interposition of tissue (eg omentum, peritoneal flap)
- ABx
- local estrogen cream to improve tissue quality

Compare & contrast the ABDOMINAL & TRANSVAGINAL approaches to VVF repair (CHART).

	Abdominal	Transvaginal
Timing of repair	- often delayed 3-6 months	- can be done immediately if no infection or complication
Fistula location and exposure	- difficult to access fistula low on trigone or near BN	- difficult to access fistula high at vaginal cuff
Location of ureter relative to fistula	- fistula near UO may need ureteral reimplant	- reimplantation may not be necessary even if fistula located near UO
sexual function	- no change in vaginal depth	- risk of vaginal shortening (eg Latzko technique)
use of adjunctive flaps	- omentum, peritoneal, rectus abdominus flaps	- Martius flap, peritoneal, gluteal skin, or gracilis myocutaneous flaps
relative indications	- large fistulae, located high in a deep narrow vagina - radiation fistulae - failed transvaginal approach - if augment or reimplant needed - unable to place in lithotomy	- uncomplicated, low fistula

List potential advantages & disadvantages of a TRANSVAGINAL approach for VVF repair

ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none"> - avoid morbidity of laparotomy - short OR time - short hospital stay + early return to work - less post-op pain - minimal blood loss - no need to bivalve bladder - can do 3 or 4 layer closure - dissection not affected by previous abdo/pelvic Sx - can do concomitant anti-incontinence or prolapse Sx - local interposition flaps are adjacent - if fails, abdominal approach still ok 	<ul style="list-style-type: none"> - lack of familiarity with vaginal approach - potential for vaginal shortening - hard to expose high or retracted fistulas near vaginal cuff in deep, narrow vaginas - requires high lithotomy position - unable to perform concomitant abdo surgery if one is required

What is involved in preparing a patient for VVF repair?

- 1) discuss trial of conservative management
- 2) consider pre-op estrogen cream to improve tissue quality, especially with vagina atrophy
- 3) decide on approach } abdominal vs vaginal
- 4) prepare for possible interposition flaps or grafts
- 5) consider C&S directed ABx for infections } limited evidence for prophylactic ABx
- 6) document sexual function/activity pre-op and discuss possibility of worsening
→ dyspareunia, vaginal shortening, harvesting of Martius flap
- 7) discuss the need for prolonged post-op urinary drainage

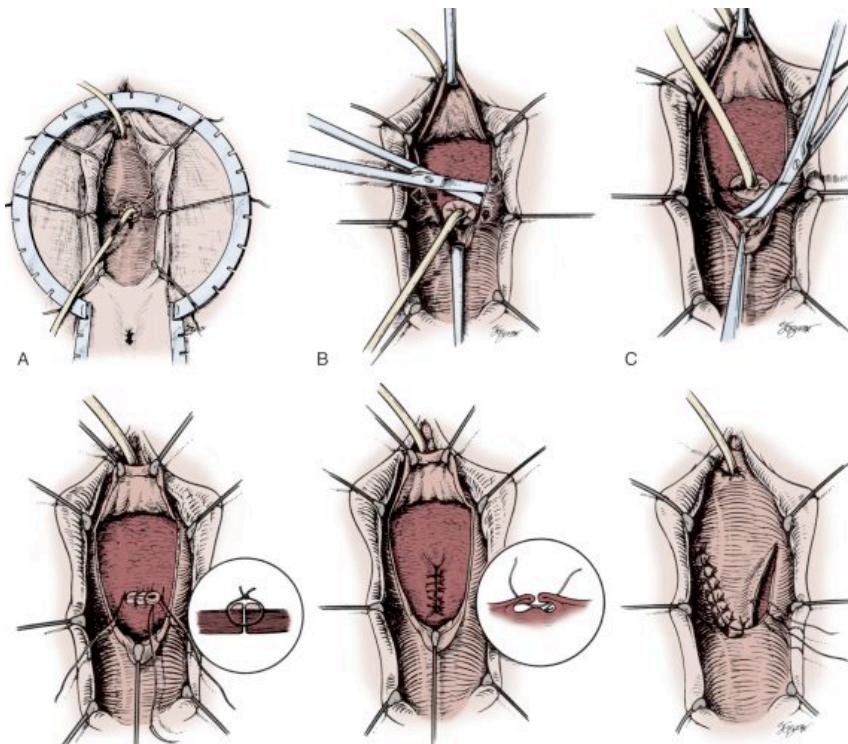
What are the popular approaches to VVF repair?

→ TRANSVAGINAL

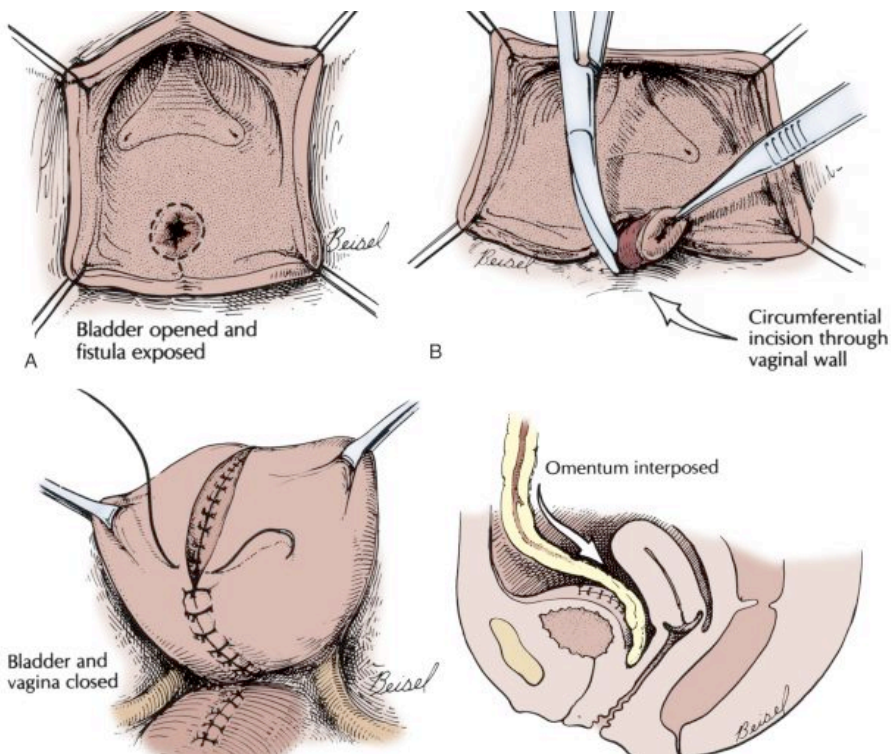
- 1) **Raz 3-layer closure** (4 layer with adjuvant flap)
 - bladder, perivesical layer, vaginal flap
 - no excision of fistula tract
 - catheter drainage x 2-3 wks followed by cytogram, post-op anti-cholinergics, vaginal packing x 24hrs, no sex for 3months
- 2) Latzko high partial colpocleisis
 - tissue surrounding VVF tract is denuded circumferentially for 1-2cm
 - denuded area is reapproximated over fistula tract
 - edges of vaginal wall reapproximated as 2nd layer +/- partial colpocleisis
 - less blood loss and no need for ureter reimplantation
 - risk of vaginal shortening and directly overlapping suture lines
- 3) Webster simple vaginal cuff excision
 - excision of fistula tract leaving funnel-shaped defect from bladder to vagina
 - defect closed in 3 or 4 layers

→ TRANSABDOMINAL

- 1) **O'Connor suprapubic approach**
 - extra-peritoneal approach to bladder
 - bladder bivalved to VVF and then tract is excised
 - bladder dissected off vagina for 2-3cm beyond VVF
 - vaginal closed, interpositional flap (omental) placed, and bladder closed in several layers
 - S/P tube + urethral catheter + anti-cholinergics
- 2) Gil-Vernet transvesical repair
 - anterior cystotomy without bivalving
 - VVF tract circumscribed and excised transvesically
 - vaginal edges mobilized from bladder, then vagina & bladder closed sequentially
 - V-flap of posterior bladder wall can be used to close large gap or to minimize overlapping suture lines
- 3) laparoscopic repair
 - limited data



→ RAZ 3-LAYER VAGINAL REPAIR OF VVF



→ O'CONOR SUPRAPUBIC ABDOMINAL REPAIR OF VVF

How successful are transvaginal & transabdominal repairs of VVF?

- >90% success rate
- outcomes worse with more complicated VVF } re-do, post-RADs, large fistulae, etc
- obstetrical fistulae associated with loss of BN & proximal urethra have high rates of persistent severe sphincteric incontinence, despite successful repair of VVF

What are the potential complications of a vaginal VVF repair?

→ intra-op

- bleeding } minimize cautery use
- **ureteral injury**

→ post-op

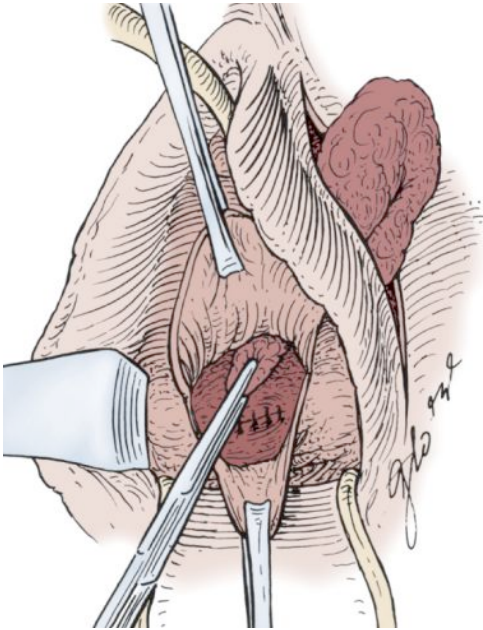
- vaginal infection
- bladder spasms
- bleeding
- vaginal shortening or stenosis
- recurrence of VVF
- dyspareunia

List the different types of adjuvant INTERPOSITION FLAPS used in VVF repair

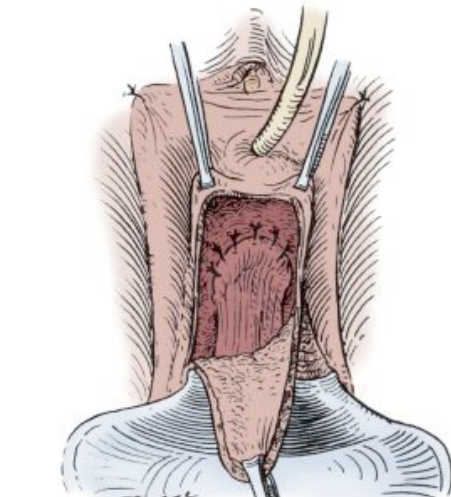
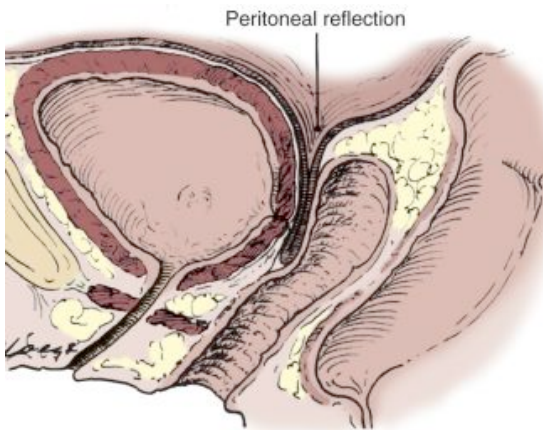
→ **good for complex fistulae } re-do's, post-RADs, obstetric fistulae, large fistulae, poor tissue quality**

→ "MOP GIRL"

- 1) **Martius flap** } for **LOW** or distal VVF (trigone, BN, urethra)
} blood supply to flap is from posterior labial vessels inferiorly (br. of internal pudendal artery), superiorly by external pudendal & laterally by obturator artery
→ lateral blood supply sacrificed during mobilization and flap is divided inferiorly or superiorly leaving flap **supplied by external pudendal or posterior labial, respectively**
} can leave JP or penrose in labial incision in operative bed
- 2) **Peritoneal flap** } for **HIGH** lying, post-hysterectomy VVF
} harvested from dissection just beyond posterior wall of bladder to access anterior cul-de-sac
} **peritoneum is NOT opened**, just mobilized and advanced
→ must close any peritoneotomy made during mobilization
- 3) **Greater Omental flap** } mainly used during **transabdominal approach** but can be used during transvaginal VVF repair if brought down during prior surgery
→ **good blood supply, easily mobilized without tension, inherent lymphatic properties, heals even in the presence of infection, and epithelialization occurs easily on its surface**
} can be mobilized with blood supply from either side but R gastroepiploic is more robust and is more caudal and so pedicle is usually taken based on this arterial supply
- 4) other flaps } **Gracilis muscle flaps**
("GIRLS") } **Intestinal flap (seromuscular)**
} **Rectus abdominis flap**
} **Labial myocutaneous flap**
} **gluteal Skin flap**
- 5) other grafts } bladder mucosa free graft



→ MARTIUS INTERPOSITION FLAP FOR VAGINAL VVF REPAIR



→ PERITONEAL INTERPOSITION FLAP FOR VAGINAL VVF REPAIR

URETEROVAGINAL Fistula

What are the RFs for ureterovaginal fistulae?

- “Fat SPERM”
- Obesity (**fat**)
- Surgery (pelvic)
- PID
- Endometriosis
- RADs
- Malignancy (pelvic)

What are the common causes of ureterovaginal fistulae (CHART)?

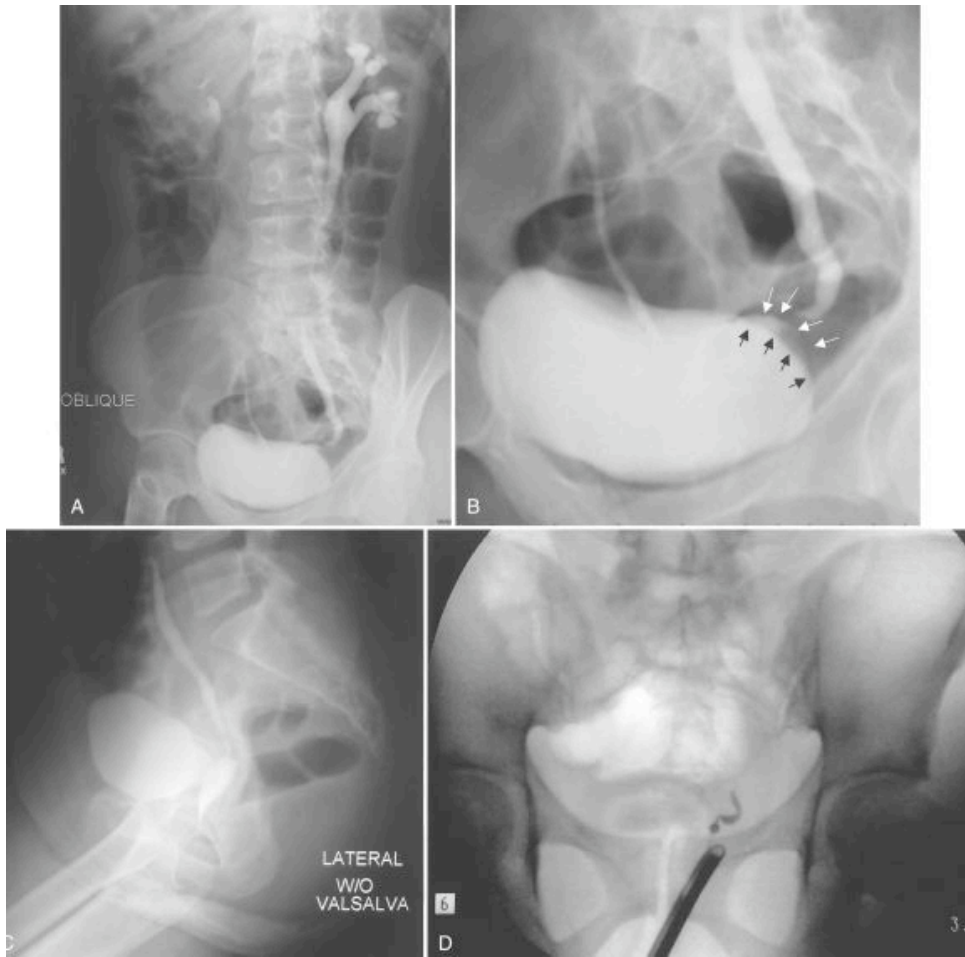
- 1) iatrogenic
 - gynecologic surgery } **laparoscopic hysterectomy (most common)**
 - (most common) } abdominal and vaginal hysterectomy
 - } radical hysterectomy (less common cf benign hysterectomy)
 - } C-section
 - } anterior colporrhaphy
 - other pelvic surgery } vascular
 - } urologic
 - } colon
- 2) other
 - locally advanced malignancy
 - RADs
 - pelvic trauma
 - chronic inflammatory diseases (eg actinomycosis)

How do ureterovaginal fistulae usually present?

- **constant urine per vagina (most common)** starting 1-4wks post-op
 - unlike VVF where it is variable, will commonly have **N voiding habits per urethra** (unless contralateral injury also)
- flank or abdominal pain
- nausea
- low-grade fever

What is the work-up for a potential VVF?

- 1) History } distinguish from SUI, urgency incontinence, overflow incontinence
 - } assess for RFs of ureterovaginal fistula (“Fat SPERM”)
 - recent Sx, PID, endometriosis, RADs, malignancies
- 2) P/E } speculum exam to assess fistula +/- vaginoscopy
 - **r/o VVF**
 - } bimanual exam to assess surrounding inflammation and timing of repair
- 3) dye tests } double dye or tampon test (Pyridium + blue dye in bladder)
 - r/o VVF and urethrovaginal fistula
 - yellow at top of tampon = ureterovaginal fistula
- 4) cystoscopy +/- VCUG } r/o VVF
- 5) imaging } IVP +/- retrograde pyelogram
 - will likely see some degree of obstruction or leakage into vagina
 - if fistula + continuity on retrograde, should attempt stent insertion



→ URETEROVAGINAL FISTULA

What are the management options for ureterovaginal fistulae?

- **goals are to rapidly resolve urine leakage, prevent urosepsis, & preserve renal function**
- **cure rates >95% } must be followed to r/o development of stricture/hydronephrosis**
- **must r/o VVF**
- 1) drainage of collecting system
 - **attempt at stenting for all cases**
 - percutaneous NT (not in Campbell's)
- 2) conservative management
 - trial of 4-6 wks of stent, if placed and leakage stops
 - **formal surgical repair indicated if unable to place stent OR persistent leak despite stent**
- 3) ureteroneocystostomy (reimplant)
 - must assess function of affected unit (especially if delayed presentation)
 - early repair is preferred } some advocate 4-8wks delay
 - +/- Psoas Hitch

URETHROVAGINAL Fistula

What are the common causes of UVFs?

→ **industrialized world } iatrogenic**

- anti-incontinence surgery
- anterior vaginal wall prolapse surgery
- urethral diverticulectomy

→ **developing world } obstructed labour**

- usually see urethral-VVF

→ other causes } pelvic RADs for malignancy

} trauma (pelvic fracture)

} vaginal neoplasms

} urethral catheter erosion

How do UVFs usually present?

→ **depends on size & location**

- small } minimal leakage
- large } continuous urine drainage
- near BN } continuous incontinence
- proximal fistula } SUI or constant incontinence
- distal fistula } may be completely asymptomatic or associated with splayed stream
- } may see vaginal voiding

What is the work-up for a potential UVF?

1) P/E } speculum exam

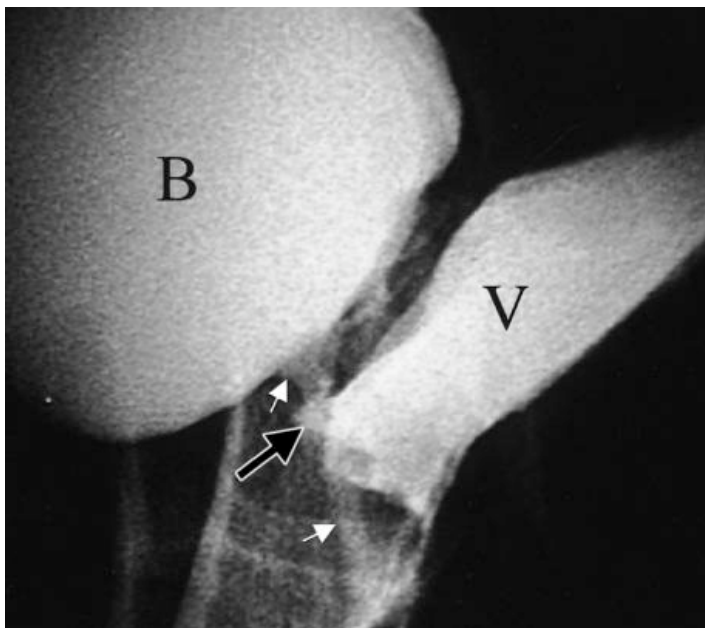
- may not be able to see small fistulae (vaginal rugation)

} look for evidence of postmenopausal atrophy (may need estrogen)

2) cystourethroscopy + VCUG } need to locate and characterize fistula

} **need to r/o VVF → occurs in 20% of cases**

3) +/- VUDS } to characterize any associated incontinence, gives anatomic info & to r/o VVF



→ VCUG OF URETHRO-VAGINAL FISTULA (normal urethra = white arrow, fistula = black arrow)

What are the management options for UVF?

- can be more difficult than VVF repair } extensive soft tissue defects
- } lack of local viable tissue for multi-layer closure
- } **success rates lower than for VVF repair**

→ timing is controversial } early vs delayed

→ consider ABx or estrogen to optimize tissue before repair

1) small fistulae

→ multi-layer closure (a la Raz) +/- Martius flap

2) larger fistulae

→ may need extensive surgery, including urethral reconstruction

3) distal fistulae without associated voiding symptoms or incontinence

→ observation

→ extended meatotomy

What is involved in the post-op care after urethrovaginal fistula repair?

- urinary drainage controversial } S/P alone, S/P + urethral catheter, urethral catheter alone

- anti-cholinergics

- drainage for 2wks post-op } VCUG prior to removal

What adjuvant flaps can be used to improve urethrovaginal fistula repair results?

→ fistula excision + vaginal advancement flap alone associated with high failure rates

- martius labial fat flap

- vaginal wall flap

- gracilis muscle flap

- rectus abdominis muscle flap

- myocutaneous flap

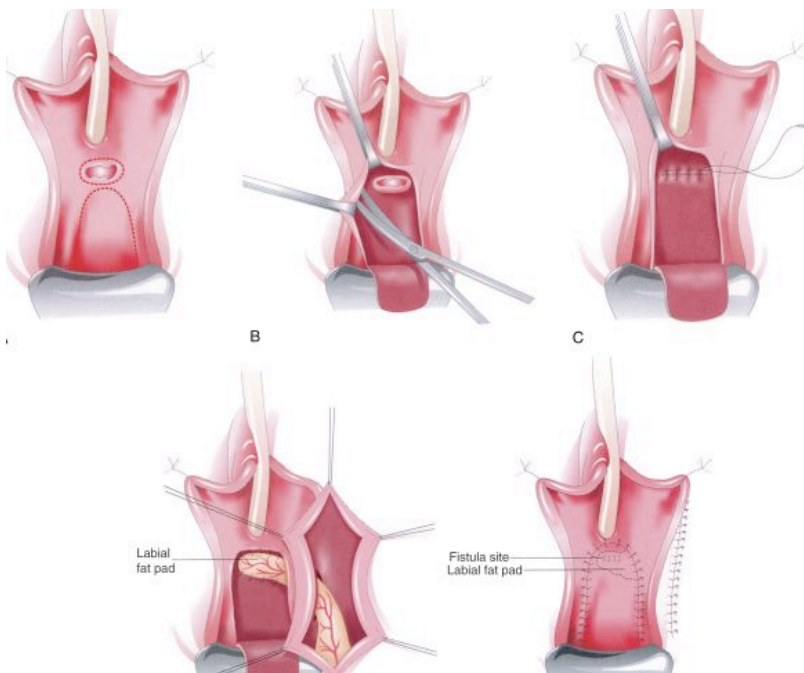
- labial skin graft

When is the best time to address SUI that is often associated with UVF repair?

- Blaivas } same time with Martius flap interposed between repair and fascial sling

- Webster } reassess after UVF repair

→ both camps agree that SUI associated with distal UVF can be fixed concomitantly



→ URETHROVAGINAL FISTULA REPAIR

VESICOUTERINE Fistula

What are the common causes of vesicouterine fistula?

→ **rare entity (~100 reported cases)**

1) **C-section (low-segment) } most common by far**

2) other obscure causes

- | | |
|----------------------------------|--|
| - abortion | - uterine rupture from obstructed labour |
| - placenta percreta | - IUD |
| - brachytherapy | - uterine artery embolization |
| - high forceps, vaginal delivery | - traumatic bladder catheterization |

How does vesicouterine fistulae usually present?

- constant urinary incontinence (incompetant cervix) } **if cervix is competent, may not have constant incontinence**
- menouria
- cyclic hematuria (must r/o endometriosis of bladder)

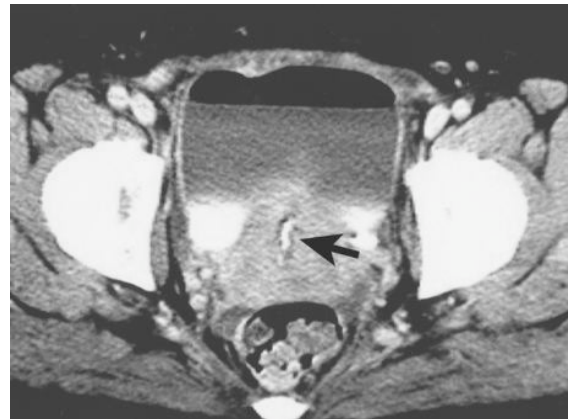
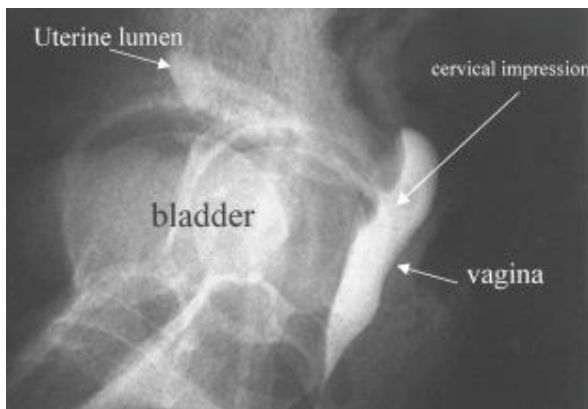
What is Youssef's syndrome?

→ presenting symptom complex of vesicouterine fistula post-low-segment C-section

- menouria + cyclic hematuria + apparent amenorrhea + infertility + urinary continence

How is the Dx of vesicouterine fistula made?

- cystoscopy } midline lesion on posterior wall
 } cytology may show **endothelial cells**
- imaging } cystogram will outline uterus
 } hysterosalpingogram will outline bladder
 } IVP or CT urogram to r/o concomitant ureteral injury



What are the management options for vesicouterine fistula?

→ conservative management

- 1) fulguration of tract + bladder drainage } for small, immature fistulae
- 2) hormonal induction of menopause } involution of puerperal uterus

→ surgical management

→ **depends on fertility wishes of patient**

- 1) transabdominal hysterectomy + bladder closure
 - stents to identify ureters
 - omental flap over bladder closure to prevent VVF
- 2) transabdominal vesicouterine fistula repair (a la O'Connor VVF repair)
 - bladder bivalved to fistula and tract excised
 - uterus and bladder separated and closed separately
 - interpositional flap placed between two organs

Vesicoenteric Fistula

- diverticulitis (70%) } **most common cause overall, especially for colovesical**
 } 2% with diverticulitis develop a colovesical fistula
- malignancy (10-15%) } colorectal Ca accounts for most (colovesical fistula)
- Crohn's (5%) } usually get ileovesical fistulae (**most common small bowel fistulae to bladder**)
 } 2% with Crohn's get enterovesical fistulae
- RADs
- infection
- appendiceal abscess
- trauma } iatrogenic VS external penetrating trauma
- FB

- **pneumaturia (50-70% - most common)**
- **fecaluria (36-51%)**
- frequency, urgency, dysuria (~45%)
- fever and chills (~40%)
- non-specific GI symptoms (25%)

- abdo pain (25%)
- recurrent UTIs
- hematuria
- orchitis
- urine per rectum

- 1) Hx & P/E } assess for RF's and r/o acute infection/sepsis
- 2) cystoscopy } **abN findings found in >90% but Dx made in only ~40%**
 } Bx to r/o malignancy
- 3) **CT with contrast** } **most sensitive & specific overall (90-100% diagnostic)**
 } triad of findings suggestive of colovesical fistula
 - a) bladder wall thickening adjacent to thickened loop of colon
 - b) air in bladder (without recent instrumentation)
 - c) presence of colonic diverticula
- 4) cystogram & Barium enema } less likely to demonstrate the fistula

- test after non-diagnostic Barium enema
- first voided urine after Barium enema is centrifuged and then examined under x-ray
- **radiodense particles in urine is considered a +ve test** } evidence for a vesicoenteric fistula

- conservative management
 - for non-toxic, minimally symptomatic patient with non-malignant cause (eg Crohn's)
 - NPO + TPN + ABx + Foley
- operative management
 - goal is to separate & close involved organs w/ minimal anatomic disruption & N long-term fxn
 - approach based on location, cause of fistula, patient's general condition, presence of pelvic abscess, presence of colonic obstruction
 - 1) single stage } removal of fistula + resection of bowel segment + closure of organs
 - 2) 2-stage } removal of fistula + closure of organs + proximal diverting colostomy

Ureteroenteric Fistula

What are the common causes of ureteroenteric fistulae?

- **IBD (most common cause) } terminal ileum is most likely segment**
- diverticulitis
- stones
- RADs
- TCC
- trauma } iatrogenic VS external
- TB

How are ureteroenteric fistulae diagnosed?

- presentation } **bowel symptoms more common** than urinary tract symptoms
- investigations } retrograde pyelogram or CT urogram

What is the management of ureteroenteric fistulae?

- assess renal fxn prior to making definitive decision } if malignancy related, Rx is different
- 1) ureterolysis + possible bowel segment resection + stent
- 2) ureteral segment resection + UU + possible bowel segment resection + stent
- 3) nephrectomy + possible bowel segment resection

Pyeloenteric Fistula

What are the common causes of pyeloenteric fistulae?

- R-sided fistulae usually involve the duodenum, L-sided usually descending colon
- **chronic inflammatory disease (eg XGP, IBD) } most common cause**
- trauma } iatrogenic (eg PNL)
 - becoming more common
 - } external
- malignancy
- ulcer disease
- ingested FBs
- complex stones

How are pyeloenteric fistulae diagnosed?

- presentation } most present with non-specific symptoms
 - fever and malaise
 - urinary frequency
 - pyuria
 - non-specific GI symptoms
 - flank mass
 - flank tenderness
- investigations } retrograde pyelogram, IVP, nephrostogram, barium swallow/barium enema

What is the management of pyeloenteric fistulae?

- historically treated with Nx + closure of bowel
- **assess renal function**
- 1) large NT + ureteric stent + bowel rest + TPN + ABx + removal of any FBs (stone, ingested)
- 2) if poorly functioning kidney, Nx + closure of bowel

Rectourethral Fistula

→ includes 2005 AUA Update

What are the common causes of rectourethral fistulae?

- congenital rectourethral fistulae } associated with imperforate anus
- acquired } iatrogenic
 - **Rad P (most common cause)**
 - TURP
 - prostate cryotherapy, brachytherapy, HIFU
 - pelvic RADs
 - anorectal surgery
 - urethral instrumentation
- } external trauma
- } malignancy
 - locally advanced PCa or rectal Ca
- } inflammatory/infectious
 - ruptured prostatic abscess
 - IBD
 - TB

How common are rectourethral fistulae after Rad P?

- occurs in <0.5% of men post-RP
- usually at level of anastomosis and associated with unrecognized rectal injury
- extremely uncommon if rectal injury (~1-2%) is recognized intra-op and repaired
- RP is most common cause b/c so common, but rectourethral fistulae are not common post-RP
- prior pelvic RADs, rectal surgery, or TURP increases risk of rectourethral fistula post-RP

How common are rectourethral fistulae after other prostate procedures?

- cryotherapy } 0.5 to 2% after primary prostate cryo
- } 3% after salvage prostate cryo
- brachytherapy } about 0.5%

How are rectourethral fistulae diagnosed?

- presentation } variable
 - fecaluria
 - hematuria
 - UTIs
 - palpable tract on DRE
 - urine from rectum
 - N/V
 - fever
 - peritonitis, sepsis
- investigations } cystourethroscopy, sigmoidoscopy
 - consider Bx if malignancy an issue
- } VCUG, RUG
 - definitive diagnosis with anatomic detail/info
- } retrograde pyelogram, CT urogram, IVP
 - r/o ureteral injury

What are the management options for rectourethral fistulae?

→ **most will require surgical repair**

→ conservative management

- mainly for post-RP } Foley + NPO + TPN +/- fecal diversion
- } fulguration of fistula tract +/- fibrin glue
- } endoscopic suturing +/- fibrin glue

→ surgical management

- 1-stage repair } iatrogenic, small fistulae not assoc'd w/ infection, abscess, or poor bowel prep
- staged repair +/- fecal diversion } large & complex (RADs, local/systemic infection, immunocompromised, poor bowel prep, etc)
- } debate whether to divert feces before GU tract repair, after GU tract repair, or at all

What are the indications for fecal diversion?

- poor control of symptoms with ABx + urinary diversion
- persistence of fecaluria despite conservative measures in presence of sepsis

What are the relative contraindications to a single stage repair?

- RADs
- need for surgical diversion due to uncontrolled local & systemic infection
- extensive or large rectal injuries leading to fistula formation
- immunocompromised states
- inadequate bowel prep at time of definitive closure
- prior anorectal dysfunction

What are the different repairs for rectourethral fistulae?

→ transrectal approach

- 1) York-Mason } transrectal, trans-sphincteric (posterior)
 - } staged repair with fecal diversion prior to fistula repair
 - occasional can be done as single stage
 - } good results with low morbidity

→ transanal approach

- 1) Latzko } transanal, sphincter sparing
 - } rectal mucosa surrounding fistula denuded + 3 layer closure over tract site
 - } poor exposure
- 2) rectal advancement flaps

→ perineal approach

- 1) +/- interposition flaps } familiar to urologists with access to flaps
 - gracilis m., dartos m., penile skin, levator m., bladder
 - } excellent results

→ transabdominal approach

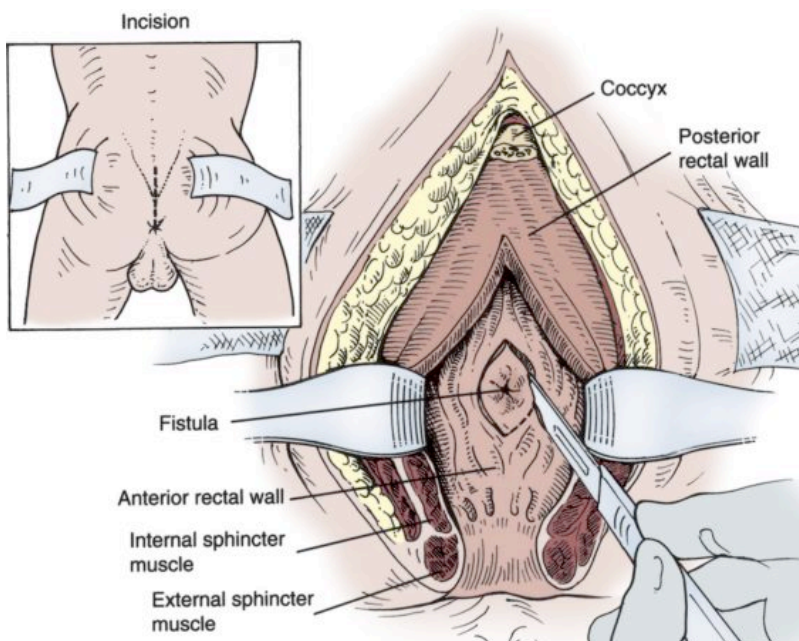
- 1) transabdominal repair } bad outcomes and morbid
 - risk of urinary & fecal incontinence, poor exposure

What are the special considerations for rectourethral fistulae post-brachy or post-cryo?

- may be extremely hard to fix } large fistulae with +++ induration, fibrosis, ischemia
- may need urinary diversion in some cases

List the advantages & disadvantages of different approaches to rectourethral fistula repair.

Repair Type	Advantages	Disadvantages
Posterior transrectal transphincteric (York-Mason)	Bloodless, excellent exposure, scarless dissection, minimal risk of ED or incontinence, availability of tissue for interposition	Inability to repair concurrent urethral stricture through the same incision
Transanal (Latzko)	Eliminates cutaneous incisions, no increased risk of ED	Difficult exposure, lack of instrument maneuverability
Perineal	Easy access to posterior urethra through familiar tissue planes, moderate exposure of fistula, allows concomitant repair of urethral stricture, availability of tissue for interposition	Visualization of fistula tract, associated dissection can be difficult due to scarring, risk of injury to rectum and urethra, development of secondary ED and incontinence
Transabdominal	Allows for omental interposition, facilitates colonic pull-through procedures and treatment of concomitant abdominal injuries	Poor exposure and maneuverability, often requires second incision to manage urethral injuries, increased risk of fecal and urinary incontinence
Anterior transanorectal	Bloodless approach, excellent exposure to fistula, amenable to tissue transposition, access to posterior urethra affords concomitant treatment of strictures	Risk of injury to neurovascular bundles with secondary ED
Endoscopic	Minimally invasive approach, no cutaneous incision, can be performed as an outpatient	Durability and success of the procedure not yet determined
Posterior-sagittal	Excellent exposure, facilitates rotation of rectum to offset involved tissues	Denervation injury to anal sphincter



→ TRANSRECTAL, TRANSPHINCTERIC YORK-MASON REPAIR OF RECTOURETHRAL FISTULA

What are the management options for ureterovascular fistulae?

→ **consider early surgical intervention, especially because most present with severe hemorrhage + hypoTN and investigations are often non-diagnostic**

→ vascular surgery consult essential

→ vascular side

- embolization \
- primary repair } limb salvage is important
- ligation +/- bypass / consideration
- endovascular graft

→ urologic side } repair & reconstruction often complicated due to hx of RADs, malignancy, vascular disease, or prior surgery

} must assess renal function

- UU
- TUU
- cutaneous ureterostomy
- perc NT + ureteral ligation
- NX } if poorly functioning kidney

OTHER URINARY TRACT FISTULAE

What are nephropleural fistulae?

→ causes } infection (eg XGP, TB, renal abscess)

} trauma

} stones

} PNL (supracostal access)

→ presentation } cough

} urine-like taste in mouth

} fever

} flank pain

} rarely presents with recurrent lung abscess

→ Rx } percutaneous drainage of any associated abscess

} ABx for any associated infections

} relief of any urinary tract obstruction

} some percutaneous access related iatrogenic fistulae can be managed non-operatively

} surgical exploration + interposition of healthy tissue

} Nx if poorly functioning kidney

What are urocutaneous fistulae?

→ causes } renocutaneous

- chronic pyelonephritis, external trauma, iatrogenic (PNL, PNx, etc)

} ureterocutaneous or vesicocutaneous

- often iatrogenic, even therapeutic

- external penetrating trauma

- malignancy

- chronic infection

→ Rx } renocutaneous

- Nx if poorly functioning

- ureteric stenting

} ureterocutaneous, vesicocutaneous

- r/o distal obstruction

- if associated with infection, find source and treat

- ensure adequate nutrition

- r/o occult malignancy

Chapter #73 – Bladder & Urethral Diverticula

BLADDER DIVERTICULA

What is a bladder diverticulum?

- herniation of bladder urothelium through muscularis propria of bladder wall
- on histology } urothelium + lamina propria + scattered thin muscle fibers + adventitial layer
 - few circular fibers of middle layer of detrusor are found around neck of diverticulum
 - **scattered muscle fibers are non-functional } poor emptying**
 - usually has pseudocapsule outer shell

What is the classification of bladder diverticula?

- congenital
 - presents during childhood } almost exclusively in boys
 - usually solitary } located posterolateral to ureteric orifice
 - usually not associated with trabeculated bladder
 - high prevalence of associated VUR
- acquired
 - usually presents in adulthood } much more common in M
 - } can present in kids w/ neurogenic voiding dysfxn, PUV, etc
 - usually multiple } also often located near UVJ but can be anywhere
 - most often associated with BOO and urethral strictures
 - can also be iatrogenic } inadequate closure of muscle layers post-cystotomy

What is a Hutch diverticulum?

- acquired bladder diverticulum that encompasses u/o in setting of neurogenic bladder + VUR

Which syndromes have been associated with congenital Hutch diverticula?

- “FEW Men”
- Fetal alcohol syndrome
- Ehlers-Danlos syndrome
- Williams syndrome
- Menkes syndrome (kinky-hair or copper deficiency syndrome)

How do bladder diverticula usually present?

- non-specific urinary findings common
- often found on work-up of LUTS, hematuria, UTI
- also found incidentally during imaging

How common are bladder tumours found in bladder diverticula?

- **1-10% have associated malignancy in diverticulum** } TCC (75%)
 - } SCC (20-25%)
- no muscularis propria } easier to go from T1 to T3
- staging at presentation is one of the most important prognostic factors
 - staging after TURBT can be difficult and is often inaccurate
 - risk of perforation and seeding
- historically worse prognosis than non-diverticular TCC
 - some recommend no TURBT } open exploration + partial or radical cystectomy
 - some advocate for diverticulectomy alone for low-grade, low-stage TCC

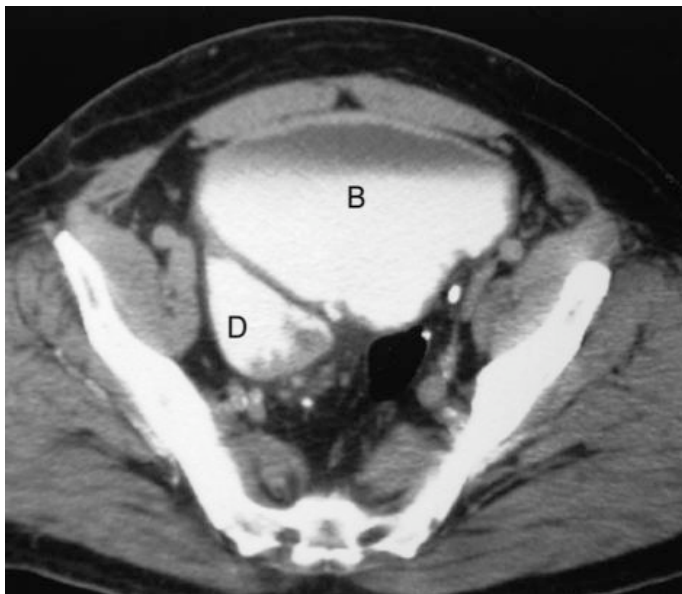
What is the work-up for suspected bladder diverticulum?

- 1) history and P/E } voiding hx, LUTS, hematuria, surgical hx
 } abdominal masses, inguinal hernias, DRE
- 2) lab tests } urine R&M, urine C&S, cytology (if non-operative management)
- 3) cysto } must inspect entire interior of diverticulum to r/o stones & tumours
 } make note of location and proximity to BN and u/o
 } take urine cytology from diverticulum
- 4) imaging } VCUG
 → gives info on anatomy, location, size, assoc'd VUR, emptying of diverticulum w/ voiding
 } CT urogram or MRI
 → can better assess narrow-necked diverticulum
 → can also assess for masses, stones inside diverticulum
 → also assesses upper tracts for asymptomatic/silent hydro
 } +/- IVP
 → can assess for asymptomatic/silent hydro
 → often see medial deviation of distal ureter (lateral can occur too)
 } +/- VUDS
 → if voiding dysfunction is suspected or hydroureteronephrosis is found
 → bladder contractility may appear diminished due to "pressure sink" effect of diverticulum

What are the indications for surgical management of bladder diverticula?

→ "Cut Out Very Slowly SIR"

- Rx of cause of acquired bladder diverticula is essential } ie treat BOO first or concomitantly
- size is NOT an indication
- Cancer
- Obstruction of upper tracts
- VUR (ipsilateral)
- Stones
- Symptoms persist
- Infections recur
- Renal deterioration



→ CT SCAN OF BLADDER DIVERTICULUM WITH FILLING DEFECTS

What are the management options for bladder diverticula?

- **must always treat cause before or concomitantly** } eg TURP
- initial treatment of cause may improve emptying of diverticulum and if no complicating factors are present (stones, VUR, UTIs, malignancy, etc) then surveillance may be option
- if malignancy suspected or found, treated differently
- 1) observation
 - if no complications occur } symptoms, stones, VUR, UTIs, malignancy
 - if unable or unwilling to undergo surgical management
 - consider CIC
 - routine surveillance with cystoscopy + upper tract imaging
- 2) endoscopic management
 - if complications are present but poor surgical candidate
 - for those undergoing TURP
 - resection of narrow neck +/- fulguration of urothelium within diverticulum
 - to allow improved emptying
- 3) diverticulectomy
 - can also perform suprapubic prostatectomy concomitantly
 - must take note of adjacent structures } vessels, ureters, bowel, etc
 - should remove all diverticula
 - +/- ureteric stents
 - transvesical approach
 - Hugh Hampton Young } for small diverticula w/o extravesical adhesions
 - } Allis used to evert diverticulum into bladder
 - } excised circumferentially + defect in bladder closed
 - } watch out for other adjacent organs that can be pulled into bladder with diverticulum
 - submucosal excision } for larger diverticula or if extravesical adhesions
 - } diverticular neck circumscribed and plane b/w wall of diverticulum & surrounding fibrous capsule is defined
 - can pack diverticulum with gauze
 - } with traction on neck, diverticulum is dissected from surrounding tissue and delivered into the bladder
 - } diverticulum is removed and bladder defect closed
 - combined transvesical & } for large diverticula + considerable peri-diverticular inflammation
 - extraperitoneal approach } for diverticula encompassing ureter
 - } diverticular neck circumscribed and gauze used to pack diverticulum
 - } diverticulum opened from outside bladder & dissection of tic carried out completely extravesically
- 4) laparoscopic diverticulectomy
 - evolving role

What are the potential complications associated with bladder diverticulectomy?

- **ureteral injury } worst**
- bleeding
- infection
- prolonged urinary extravasation
- urinary fistula
- bowel injury
- storage symptoms

FEMALE URETHRAL DIVERTICULA

What are the main anatomic structures supporting the female urethra?

- lies within **urethropelvic ligament** } **endopelvic fascia** on abdominal side
 } **periurethral fascia** on vaginal side
- suspended by urethropelvic ligament to **pelvic sidewall & pelvic fascia** } tendinous arc of obturator muscle

Describe the female urethra.

- on avg 4cm from BN to vaginal vestibule
- **thick layer of inner longitudinal smooth muscle** travels along urethra from BN to meatus
→ **no circular smooth muscle sphincter identified**
- **EUS invests the distal 2/3 of the female urethra**
→ omega shaped distally as fibers fan off laterally onto anterior vaginal wall
- urethra is suspended beneath pubis by suspensory ligament of clitoris (anterior urethral ligament) & the pubourethral ligaments (posterior urethral ligament)
- EUS receives dual somatic innervation like in men → **pudendal & pelvic somatics**

What are the important anatomic features of the urethra & periurethral tissues?

- transitional cell urothelium proximally
 - nonkeratinized stratified squamous cell urothelium distally
 - enveloped by smooth & skeletal muscle and fibroelastic tissue
 - periurethral glands found in vascular lamina propria (submucosal) along entire length **posterolaterally**
 - most prominent over distal 2/3 of urethra
 - Skene's glands are largest & most distal of periurethral glands, draining outside the urethral lumen, lateral to the meatus (homologue of prostate in males)
- ➔ **MOST ACQUIRED FEMALE URETHRAL DIVERTICULA COME FROM ABNORMAL PERIURETHRAL GLANDS**

What is the blood supply to the female urethra?

- proximal urethra } superior & inferior vesical arteries
- distal urethra } vaginal artery (terminal branch of inferior vesical)

What is the lymphatic drainage of the female urethra?

- proximal urethra } external + internal iliac nodes
- distal urethra } superficial + deep inguinal nodes

What is the innervation of the female urethra?

- somatic innervation } pudendal nerve (S2-S4) + pelvic somatics
 - afferents to pelvic splanchnics
- parasympathetic fibers found throughout smooth muscle } few sympathetics found

What is a urethral diverticulum?

- **epithelialized cavity with a single connection to the urethral lumen**
 - lined by columnar, cuboidal, stratified squamous, or transitional cells
 - sometimes there is no epithelium, just fibrous tissue lining diverticulum
- size may vary from a few mm's to several cm's } size may vary over time also
- **90% have ostium in posterolateral location in mid or distal urethra**
- sphincteric compromise may coexist
 - may be due to diverticulum or due to another cause

What are the causes of urethral diverticula?

- congenital } extremely rare and likely a different entity
 - congenital anterior urethral diverticula in boys
 - Skene's gland cysts
 - ectopic ureter into Gartner's duct cyst
 - aborted urethral duplication
- acquired } from abN periurethral glands likely involving infectious process
 - reinfections, inflammation, and recurrent obstruction of neck of cavity
- } urethral trauma (childbirth, instrumentation)

How common are female urethral diverticula?

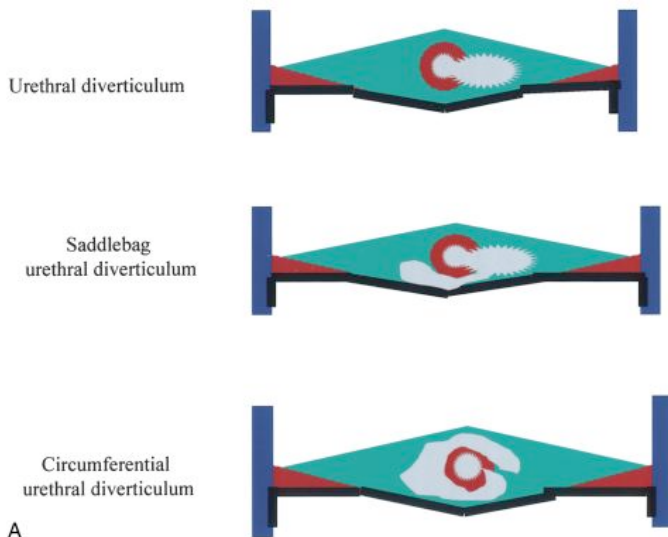
- true prevalence unknown } approximately 1-5%
- may be more common in blacks

How do urethral diverticula usually present (also includes CHART)?

- **usually presents during 20's to 60's with nonspecific LUTS**
- **classic presentation of 3 D's } dysuria + dyspareunia + dribbling (postvoid)**
- other common symptoms } frequency & urgency, pelvic/urethral pain, UTIs (*E. coli* & *N. gonorrhoeae*)
- can also present with:
 - vaginal or pelvic mass
 - vaginal or urethral discharge
 - urinary retention
 - hematuria
 - incontinence (SUI or urgency)
- ~20% are asymptomatic on presentation (incidental finding)
- size does not correlate with symptoms
- more likely to become symptomatic during pregnancy

What are the 3 different types of urethral diverticula?

- 1) **simple** urethral diverticulum
- 2) **saddlebag** urethral diverticulum
- 3) **circumferential** urethral diverticulum



→ FEMALE URETHRAL DIVERTICULA

What is involved in the work-up for suspected female urethral diverticulum?

- List the advantages & disadvantages of different imaging modalities used to assess female urethral diverticula?**

	ADVANTAGES	DISADVANTAGES
Double-balloon PPU	- not dependent on patient voiding	- specialized equipment needed - invasive - can't see non-communicating diverticula
VCUG	- familiar test to many	- invasive - dependent on patient voiding - low flow rate may not fill diverticulum well - can't see non-communicating diverticula
U/S	- cheap - relatively non-invasive - no radiation - not dependent on patient voiding	- poor anatomic detail - operator dependent
MRI	- non-invasive - high-resolution - not dependent on patient voiding - no radiation	- expensive - some MRI contraindications

What are the different classification systems for urethral diverticula?

- 1) Leach L/N/S/C3 } location, number, size, configuration, communication site & continence status
- 2) location based } distal, proximal
- 3) Leng-McGuire } based on presence or absence of a preserved periurethral fascial layer

What are the indications to repair a female urethral diverticulum?

- symptomatic patients } dysuria, postvoid dribbling, dyspareunia, recurrent UTIs, pelvic pain attributed to urethral diverticulum
- concomitant SUI } for combined procedure
- diverticular stone
- elective for cosmetic reasons, risk of malignancy, personal reasons

What are the management options for female urethral diverticula?

- 1) conservative therapy } postvoid stripping of urethra + suppressive ABx
 } long-term surveillance
- 2) surgical therapy
 - ➔ **transvaginal repair +/- anti-incontinence surgery** } **excision + reconstruction**
 - } **most common approach**
 - transvaginal marsupialization (Spence) } only for distal diverticula
 - transurethral marsupialization
 - endoscopic unroofing
 - fulguration

What are the principles of transvaginal urethral diverticulectomy (CHART)?

- 1) mobilization of well vascularized anterior vaginal wall flap
- 2) preservation of periurethral fascia
- 3) identification & excision of neck of urethral diverticulum or ostium
- 4) removal of entire urethral diverticulum wall or sac (mucosa)
- 5) watertight urethral closure
- 6) multi-layered, non-overlapping closure with absorbable suture
- 7) closure of dead space
- 8) preservation or creation of continence

What is involved in pre-op preparation prior to repair of urethral diverticulum?

- prophylactic ABx + pre-op iv ABx
- topical estrogen cream x few wks pre-op to improve tissue quality
- **assess for concomitant SUI**
- pre-op counseling re: improvement of symptoms } often but not always improved or cured

What are the main points of a transvaginal excision and reconstruction for female urethral diverticulum?

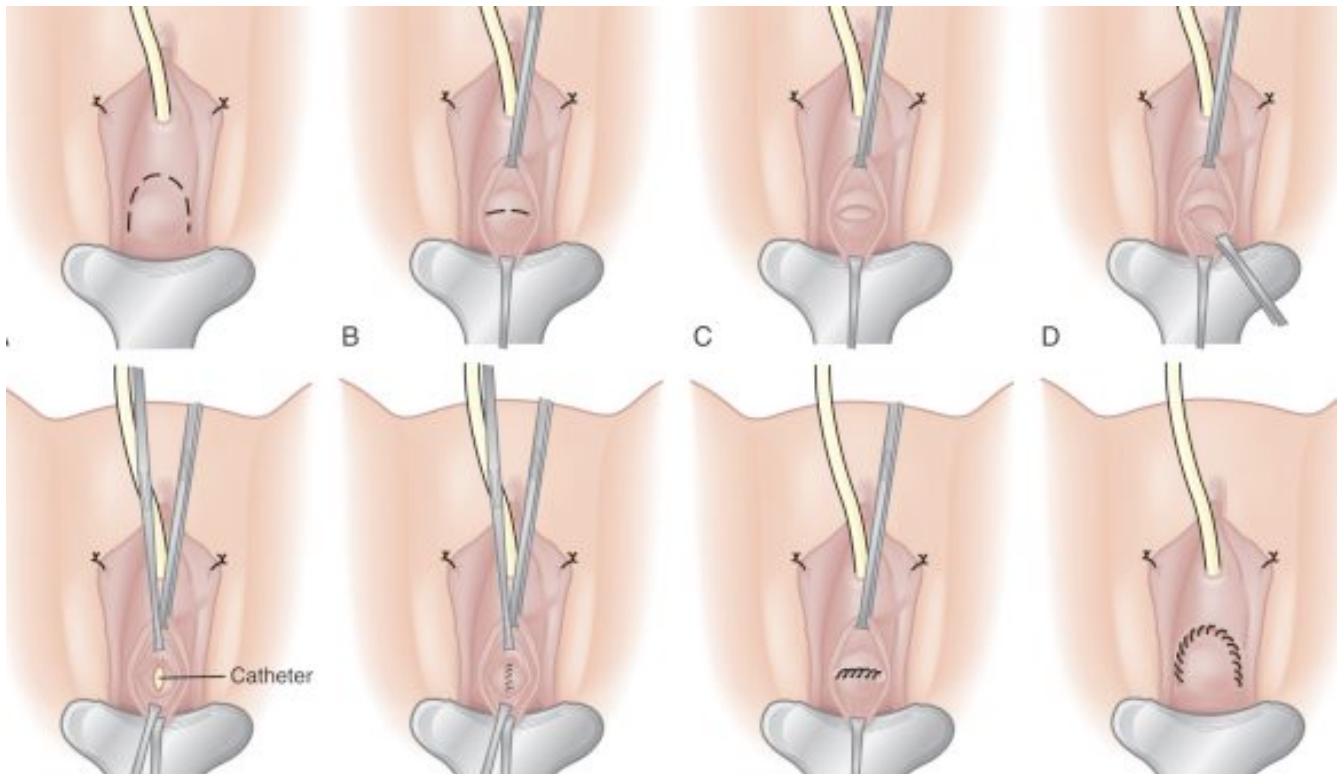
- lithotomy + weighted vaginal speculum + Scott retractor } +/- posterior episiotomy
- foley insertion +/- S/P tube insertion
- inverted U or inverted T incision on anterior vaginal wall
- develop anterior vaginal wall flaps by careful dissection b/w vaginal wall & periurethral fascia
 - preserve periurethral fascia
 - avoid entrance into urethral diverticulum
- incise periurethral fascia transversely and carefully develop proximal & distal layers
- grasp diverticulum and dissect down to origin on urethra
- remove entire mucosalized surface of diverticulum
 - to prevent recurrence
- closure of urethra
 - if diverticulum extends circumferentially around urethra, segmental resection may be required
 - complex reconstruction
- closure of periurethral fascial flaps perpendicular to urethral closure line
 - +/- interpositional flap (eg Martius)
- closure of anterior vaginal wall flap

What are the indications for an interpositional flap during urethral diverticulectomy?

- poor quality tissues
- attenuated periurethral fascia
- significant inflammation seen intra-op
- radiation hx
- re-do

What is the recommended post-op care following urethral diverticulectomy?

- vaginal packing and ABx for 24hrs
- home with anti-muscarinics
- pericatheter VCUG in 2-3 wks



→ URETHRAL DIVERTICULECTOMY } TRANSVAGINAL EXCISION + RECONSTRUCTION

What are the potential complications following urethral diverticulectomy?

→ intra-op

- bleeding
- urethral injury
- bladder injury

→ post-op

- urinary incontinence (1-16%)
- recurrent urethral diverticulum (1-25%)
- urethral stricture (~5%)
- urethrovaginal fistula (1-8%)
- recurrent UTIs
- vaginal scarring or narrowing (dyspareunia)
- hypospadias, distal urethral necrosis

What associated conditions have been found in urethral diverticulum?

→ "MENS"

- **Malignancy** } **adenocarcinoma most common**, then TCC, followed by SCC
 - if suspected should always do excision + reconstruction
 - at the very least, perform Bx with non-excisional Rx
 - unclear whether cystourethrectomy +/- adjuvant RADs is better than local excision + RADS
- **Endometriosis**
- **Nephrogenic adenoma**
- **Stones** (4-10%)

What is the DDX of a periurethral mass?

→ non-malignant

- urethral diverticulum
- vaginal leiomyoma (benign mesenchymal tumour that is estrogen dependent)
 - Rx - excision
- Skene's gland cyst/abscess (distal and don't communicate with urethral lumen)
 - Rx - aspiration, marsupialization, I&D, simple excision } usually symptomatic
- Gartner's duct cyst (Wolffian remnant)
 - Rx - upper tract imaging (renal anomalies)
 - observation if asymptomatic
 - simple excision or marsupialization
 - specialized treatment if associated with functioning renal moiety
- vaginal wall cyst (mullerian, epidermoid cyst, Gartner's duct, endometriotic, etc)
 - Rx - simple excision if symptomatic
- urethral prolapse (beefy red lesion surrounding urethral meatus)
 - Rx - medical (estrogen, sitz baths) or surgical (cauterization, ligation around Foley, complete excision)
- urethral caruncle (red, symptomatic mass at meatus that can thrombose - covered by transitional or squamous epithelium)
 - Rx - medical (estrogen, sitz baths) or surgical (excision)
- prolapsed ureterocele (paeds)

→ malignant

- urethral tumour } SCC most common distally
- tumour in urethral diverticulum } adenocarcinoma most common, then TCC & SCC
- adenocarcinoma of Skene's gland

What other disease have been associated with urethral caruncles?

- intestinal metaplasia
- TB
- melanoma
- lymphoma

Which patient population is prone to urethral prolapse?

- young black females
- post-menopausal women

Chapter #74 – Surgical Treatment of Male Sphincteric Urinary Incontinence: Male Perineal Sling & AUS

GENERAL INDICATIONS

What are the goals of the male perineal sling (MPS) & AUS?

- improve QOL
- provide urinary continence
 - optimize urethral compression & coaptation while minimizing urethral ischemia
- avoid upper tract deterioration/sequelae

What are the indications for MPS & AUS?

- bothersome SUI due to ISD that fails to improve with conservative management
 - **ISD most commonly due to RP**
 - can also be due to:
 - TURP
 - pelvic trauma
 - urethroplasty
 - traumatic or acquired myelopathy
 - congenital disorders (spinal dysraphism, sacral agenesis, etc)

List contraindications to MPS & AUS?

- **ABSOLUTE** } } } “Very Difficult, SID Called Herschorn’s Office”
 - **VUR** at low pressures
 - **DSD**
 - **Strictures** (unstable)
 - **Infections** (skin, urinary, etc)
 - **Dexterity** issues (unable to operate device)
 - **Compliance** issues
 - **High pressure** contractions/storage (>40 cm H₂O)
 - **Overactivity** at low volumes
- **RELATIVE** } } } “STACI”
 - **Stones**
 - **Tissue quality** issues
 - **Anatomic abN’ities** (eg diverticulum)
 - **Cancer** (TCC)
 - **Immunosuppression**

PROSTHETICS FOR MALE INCONTINENCE

MALE PERINEAL SLING

What are the main points of MPS insertion?

- 3-4cm perineal incision made over bulbous urethra
- bulbospongiosus muscle exposed in midline
- medial aspects of descending pubic rami exposed bilaterally
- 3 titanium bone screws inserted into anteromedial aspect of each descending pubic ramus
 - preloaded with 1-0 prolene suture
- sling tied in place loosely using synthetic or organic material
- sling tension adjusted until retrograde LPP of 60cm H₂O is achieved
- wound irrigated copiously and closed in 2 layers
- catheter removed for TOV in PACU or POD #1

How successful is the MPS?

- 40-80% "cure"
- 60-90% "cure" or "improved"
- 5-35% failures

What are the potential complications of MPS insertion?

- bleeding
- infection (1-2%)
 - removal of sling is essential
 - removal of bone screws if evidence of osteomyelitis
- erosion of sling into urethra } mainly synthetic grafts
- urinary retention } usually transient only
 - managed with S/P or CIC to minimize risk of pressure-induced erosion
- perineal numbness or hyperesthesia (5-10%) } usually transient
- recurrent incontinence
 - r/o bone-anchor displacement; otherwise consider Kegels, repeat MPS, or AUS

What is the role of MPS with RADs?

- **limited data for use post-RADs**
- seems to hold up if placed before adjuvant or salvage RADs
- may have higher rates of urethral erosion & higher failure rates due to difficult to coapt bulbous urethra

What is the role of MPS with previous & subsequent incontinence treatment?

- previous periurethral collagen injections don't adversely affect outcomes of MPS
- worse outcomes in those with previous AUS } urethral atrophy + poor compliance
- **if MPS fails, best to leave it and place AUS cuff distal to sling via scrotal incision**
 - avoids dissection in scarred area
 - leaves partially functioning MPS, similar to tandem-cuff AUS

What is the role of MPS with penile prostheses?

- cylinders lie immediately in front of descending rami
 - makes exposure difficult
 - **risk of perforation of cylinder with bone screws**
- with concomitant implantation of a penile prosthesis, bone screws placed first then the prosthetic cylinders placed, then sling placed with appropriate tension

What are the RFs for post-RP urinary incontinence?

- 1) **patient age**
- 2) **pre-op voiding function**
- 3) abN detrusor contractility
- 4) prior TURP (controversial)

- 5) higher stage
- 6) **pre-op or post-op RADs**
- 7) **surgical technique (NS vs non-NS)**
- 8) surgeon experience
- 9) excessive blood loss

- post-RP } need to wait minimum 6months (r/o BN contracture)
- SUI after pelvic fracture, SCI, urethral reconstruction
- neurogenic bladder with sphincteric dysfunction
- congenital disorders (MMC, sacral agenesis, exstrophy/epispadias complex)
- last resort in females with ISD + non-neurogenic bladders

- 1) UDS +/- video } correct VUR >grade 2
- 2) cystoscopy } r/o FB, false passages, strictures, diverticulae, BN contractures
 } must wait for ≥3months after TUIBN
- 3) upper tract imaging } r/o anatomic abN'ities, stones, etc

- 1) site of cuff placement } bulbar urethra vs BN
- 2) primary incision for cuff placement around bulbar urethra } perineal vs scrotal
- 3) number of cuffs } single vs double
- 4) plane of cuff placement } periurethral vs transcorporeal
- 5) site of reservoir placement } perivesical vs superficial pouch
- 6) incision for reservoir placement } midline vs inguinal canal

- } AUS left deactivated for 6wks

List some of the modifications to the standard AUS insertion.

- transcrotal incision } implantation without hip flexion (less stretch-tension on bulbar urethra & easier dissection of spongiosum from cavernosum)
- double-cuff implantation } improved resistance for severe incontinence or cuff atrophy
- transcorporal implantation } better when dissection of spongiosum from cavernosum is very difficult due to inflammation, ischemia, or prior erosion

What is the role of tandem-cuff AUS?

- mainly for recurrent or persistent SUI due to cuff atrophy (smaller role as primary procedure)
- excellent continence rates \ **most limiting factor is availability of**
- associated with higher urethral erosion rates / **healthy urethral site**

How successful is AUS for SUI?

- ~**90% success rates in post-RP SUI**
- **AUS revision rate is ~15-20% with newer models**

What are the potential complications of AUS insertion? (includes AUA Update #40 - 2005)

- intra-op
 - bleeding
 - organ injury } urethral, bladder, rectum
- post-op
 - hematoma/hemorrhage
 - urinary retention } usually due to inflammation/edema
 - Rx → urethral catheter x 48hrs, S/P if longer
 - } late onset may mean proximal obstruction or detrusor failure
 - Rx → cysto + UDS
 - infection } higher in post-RADs patients and in re-do's (10%)
 - (1-3%) } skin pathogens most common (***S. epidermidis* or *S. aureus***) early, **hematogenous source more common >4months post-op**
 - } often presents initially as scrotal pain
 - Rx → removal of entire device VS salvage replacement
 - if erosion, need to remove device + reimplant in 3-6mos
 - erosion } early erosion due to unrecognized urethral injury or compromise
 - (1-5%) } late erosion due to urethral atrophy or urethral manipulation via activated cuff
 - } presents with dysuria, scrotal pain, swelling (extravasation), hematuria, recurrent incontinence
 - Rx → removal of entire device, catheter to heal, replacement in 3-6 mos
 - mechanical failure } loss of fluid (disconnection, perf), obstruction of tubing (kinking, debris)
 - (10%) **→ cuff most common site of leak** } better w/ newer devices
 - non-mechanical failure } most commonly due to urethral atrophy
 - Rx → reduce cuff size, place more proximally, or place tandem
 - recurrent SUI } **most common complication**
 - } early means incorrect component selection or assembly, device malfunction, unrecognized OAB, fistula, or surgical trauma
 - } delayed likely means mechanical failure or urethral atrophy; can also be OAB or cuff erosion
 - if rapid, progressive decline to pre-op level, likely mechanical failure (fluid loss from system is most common mechanical cause)
 - if slow, progressive decline then likely urethral atrophy**
 - Rx → r/o infection, mechanical failure, fluid loss
 - cysto to r/o erosion
 - UDS to r/o OAB or persistent ISD
 - if urethral atrophy, downsize cuff or replace entire device if older than >3yrs (relocate vs insert tandem-cuff)

What are some techniques to try to decrease cuff erosion?

- 1) use of newer AUS devices
- 2) use endoscopically healthy segment of urethra
- 3) use low pressure balloon reservoir
- 4) narrow-backed cuff to improve transmission of cuff pressure to underlying tissues
- 5) deactivate at night
- 6) delayed activation of cuff

List RFs for AUS cuff erosion.

- infection
- unrecognized injury to urethra at time of implantation
- anterior urethral thinning at time of implantation
- too much mechanical pressure (cuff too tight)

What is the management of diminished bladder compliance post-AUS insertion?

- decreased vesical compliance or de novo OAB is unique to kids w/ neurogenic voiding dysfxn
 - can result in upper tract deterioration
 - likely not de novo but missed OAB/poor compliance (Herschorn)
- must address abN bladder compliance before AUS insertion
 - anti-muscarinics
 - augmentation } debate b/w 2-stage VS single stage + AUS insertion (due to infection risk)

What is the management of non-mechanical failure due to urethral atrophy?

- **urethral atrophy is most common cause of non-mechanical failure**
- less common with newer cuffs
- exploration + down-sizing of cuff
- addition of tandem-cuff

What are the main points in a BN AUS insertion?

- for kids & women & men with SUI but no hx of RP
- transabdominal approach in males, transvaginal approach in females
- mobilization of BN and proximal urethra
- 2cm wide cuff placed around BN
- tubing passed through rectus muscle and fascia

What is the role of AUS insertion in females?

- generally a procedure “of last resort” } for women with ISD in non-neurogenic women
- **try suburethral sling or PVS or periurethral bulking agents first**
- transvaginal or transabdominal } BN AUS
- excellent outcomes in properly selected patients } 75-90% success rate

What is the role of AUS insertion in kids?

- **must r/o voiding dysfunction & any decreased compliance that puts upper tracts at risk**
 - 30-60% risk of upper tract deterioration with AUS placement in kids with neurogenic voiding dysfunction
- placed at level of BN
- complications more common } erosion and infection
- much worse outcomes in kids with prior BN surgery

What is the role of AUS insertion in relation to penile prostheses?

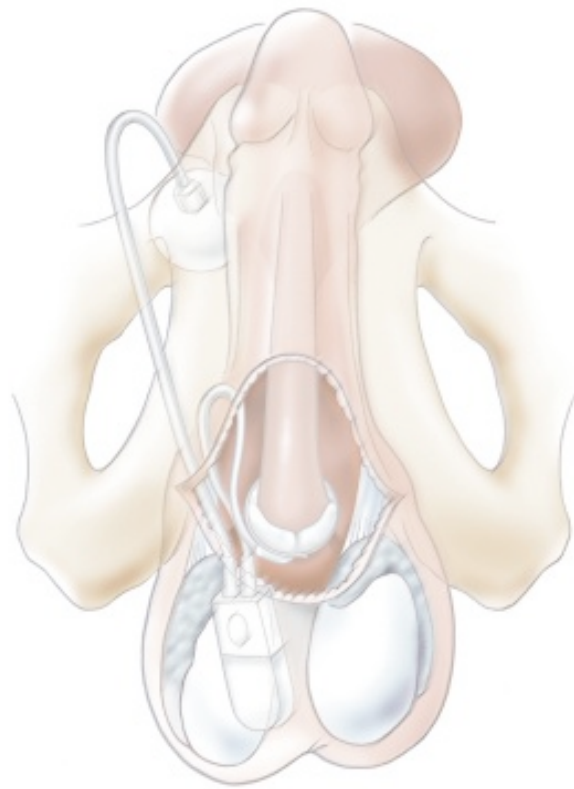
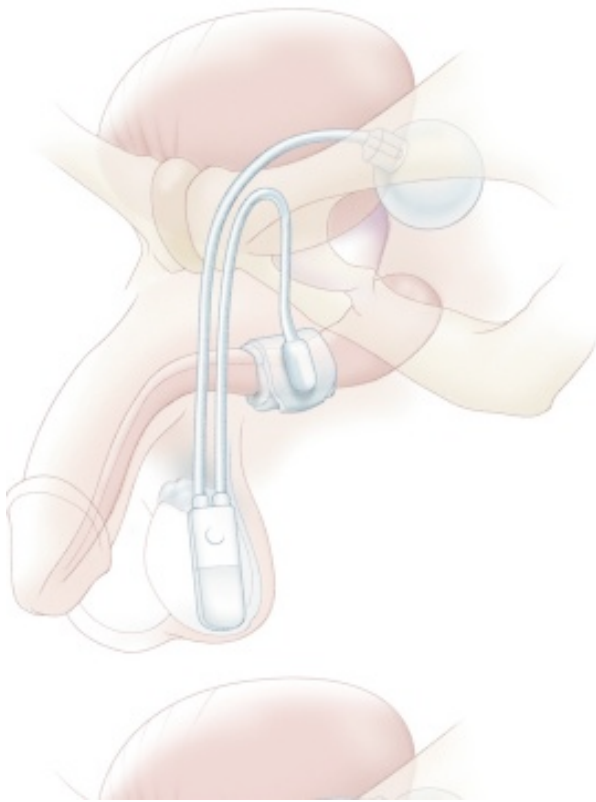
- NOT a contraindication
- can be placed simultaneously } AUS first with reservoirs and pumps on opposite sides
 - } safe and similar outcomes

What is the role of AUS insertion in relation to RADs?

- NOT an absolute contraindication
- higher risk of complications
- BUT similar continence rates

What is the role of AUS in men with previous MPS?

- if infected or eroded MPS } remove all foreign material, allow urethra to heal over catheter, re-do MPS or AUS insertion in 3-6 months
- if recurrent SUI after MPS } trans-scrotal AUS insertion
 - acts as tandem-cuff
 - } can also remove MPS and insert AUS



B

→ MALE AUS

Chapter #75 – Bladder Cancer

BASIC AND CLINICAL BIOLOGY

What are the factors that play a role in the development of bladder cancer?

- inherited or acquired alterations of DNA
 - lead to induction of oncogenes or suppression of tumour suppressor genes
 - lead to aberrations of normal mechanisms that regulate cell differentiation & proliferation
 - can result in abN repair of mutated cells or abnormal apoptotic pathways
- inherited, acquired, or anatomic factors that regulate processes such as the metabolism of chemicals and the excretion and delivery of those metabolites to potential target cells
- exposure to chemical carcinogens, viruses, or other stimuli (eg radiation)

EPIDEMIOLOGY

What are the epidemiological findings of bladder cancer?

- incidence increases with age } median age is ~70yrs of age
- ~3x more common in M
- 4th most common cancer in men after prostate, lung, colon (incidence)
 - 2nd most prevalent (after PCa)
- 9th most common among women
- rarely found incidentally at autopsy
- increasing incidence over last few decades } incidence rising faster in men
- about 2x more common in Caucasian men compared to Black men
 - 1.5x higher in white women
- blacks tend to present with more advanced stage cancers
- higher rates of non-TCC bladder cancers among blacks

What are the survival data on bladder cancer?

- higher 5 yr survival among M (esp when compared to black F)
 - F have 30% higher chance of mortality when compared to M
- stage by stage, better survival among whites
 - blacks almost 2x more likely to die from bladder cancer
- Hispanics have the best survival rates, even for invasive and advanced disease
- overall mortality from bladder cancer is decreasing despite increasing incidence
 - decrease seen more among M
- better survival rates among younger patients
 - more indolent and lower grade in younger patients
 - same risk for progression though

ETIOLOGY AND RISK FACTORS

What are the RFs for developing bladder cancer?

- 1) **cigarette smoking**
 - **4-fold increase in incidence** } back to baseline risk after ~20yrs of non-smoking
 - specific carcinogen not identified } ? 4-aminobiphenyl
 - failure to stop smoking after Dx predicts worse outcome, even for superficial TCC
- 2) occupational exposure to chemicals
 - aniline dyes (fabrics), acrolein aldehyde (textile & rubber)
 - 2-naphthylamine, 4-aminobiphenyl (benzidine)
 - aromatic amine exposure (autoworker, painter, leather worker, etc)
- 3) analgesics
 - phenacetin (similar structure to aniline dyes)
 - increased risk of renal pelvic TCC also
- 4) bacterial, viral, fungal, and parasitic infections
 - chronic UTIs associated with SCC
 - *Schistosoma haematobium* is associated with SCC and TCC
 - HPV associated with TCC only in immunocompromised hosts
- 5) bladder calculi
 - increased risk of SCC
- 6) chronic indwelling catheter
 - increased risk of SCC
 - >50% of SCI patients have invasive disease at presentation
- 7) **pelvic RADs**
 - **2-4fold increase in incidence post pelvic RADs (cervical or ovarian Ca)**
 - **usually high grade & locally advanced at time of Dx**
- 8) **genotoxic chemotherapy**
 - **cyclophosphamide ↑'s risk of bladder Ca by 9-fold (highest RR)**
 - high rate of progression } **usually high grade & muscle invasive at time of Dx**
 - acrolein aldehyde likely culprit for both hemorrhagic cystitis and bladder Ca
 - mesna may protect urothelium by binding to **acrolein** and neutralizing it
(must be given at time of chemo .. no benefit if after)
 - development of hemorrhagic cystitis DOES NOT correlate with Bladder Ca risk
- 9) Blackfoot disease
 - arsenic ingestion from contaminated water in south Taiwan
 - results in CV disease and other malignancies, including bladder TCC
- 10) Aristolochia fangchi
 - Chinese herb (*Stephania tetrandia*) for weight reduction (Belgium)
 - associated with interstitial nephropathy & urothelial TCC (**mainly upper tract TCC**)
- 11) renal transplant recipients

*** NO STRONG EVIDENCE for caffeine, sweeteners, hereditary ***

What are the RFs for developing bladder TCC? }}} "COBRA SCARS"

- | | |
|--------------------------------------|-------------------------------|
| - Cyclophosphamide | - Smoking |
| - Occupational exposure to chemicals | - Chronic UTIs |
| - Blackfoot disease | - Analgesic abuse |
| - RADs to pelvis | - Renal Tx recipients |
| - Aristolochia fangchi | - Schistosomiasis haematobium |

What are the RFs for developing upper tract TCC? }}} "COBRA SCALP"

- | | |
|--------------------------------------|----------------------|
| - Cyclophosphamide | - Smoking |
| - Occupational exposure to chemicals | - Chronic UTIs |
| - Balkan nephropathy | - Analgesic abuse |
| - RADs to pelvis | - Lynch 2 syndrome |
| - Aristolochia fangchi | - Papillary necrosis |

Which ONCOGENES have been associated with bladder cancer?

- 1) **RAS gene family (eg p21)** → associated with higher grade

Which TUMOUR SUPPRESSOR GENES have been associated with bladder cancer?

- 1) **p53 (chromosome 17p)** → **most frequently altered gene in human cancers**
 - repair of damaged DNA and pro-apoptosis of abnormal cells
 - normal p53 induces expression of anti-angiogenesis factor thrombospondin-1 (TSP-1)
 - regulated by MDM2, which degrades TP53
 - **mutation of p53 associated with more aggressive cancers**
- 2) retinoblastoma (**RB**) gene (**chromosome 13q**) → RB protein normally keeps cell proliferation in check via E2F
 - **associated w/ more aggressive TCCs**
- 3) p15, p16, p19, p27 proteins (**chromosome 9**) → cell proliferation regulated via RB protein
 - abN proteins prevent RB protein from keeping cell proliferation in check
 - **assoc'd w/ low-grade, superficial TCC**
 - **MOST COMMON genetic abN'ity**

What gene amplification & overexpression abnormalities are associated with bladder cancer?

- **increased expression of EGF receptor** } associated with **more aggressive tumours**
 - } normally there are high levels of EGF in urine, so high receptor levels cause increased EGF signalling
- **overexpression of ERBB2 oncogene product (p185)** } associated with **higher grade & stage**
 - } also associated w/ higher recurrence

What is the significance of acetylation in bladder cancer?

- amongst smokers and those with occupational exposure, pts with **slow NAT1 & NAT2 acetylator genotypes are more likely to have bladder cancer**
 - rapid acetylation of carcinogens results in detoxifying pathways

PATHOLOGY

What are the layers of the bladder?

- 1) urothelium → 3-7 layers thick
- 2) BM
- 3) lamina propria → contains muscularis mucosa AND blood vessels, lymphatics, nerves
- 4) muscularis propria → inner longitudinal, middle circular, and outer longitudinal
- 5) serosa → reflection of peritoneum

What is epithelial hyperplasia and metaplasia?

- hyperplasia } increase in # of cell layers WITHOUT nuclear or architectural abnormalities
- metaplasia } change in epithelium with squamous or adenomatous development

What is atypical hyperplasia?

- similar to epithelial hyperplasia but increase in # of cells WITH nuclear or architectural changes
- overactive atypia and atypia of unknown significance have **VERY LOW MALIGNANT POTENTIAL**

What is epithelial dysplasia?

- epithelial changes that are intermediate between normal urothelium and CIS (severe dysplasia)
- NO increase in # of cell layers or mitotic figures
- **15% risk of developing high grade TCC**

What are Von Brunn's nests?

- islands of benign-appearing urothelium in the lamina propria
- cystitis cystica is von Brunn's nests in which urothelium in centre of nest has undergone eosinophilic liquefaction
- **cystitis glandularis** is von Brunn's nests in which urothelium has undergone glandular metaplasia (goblet cells)
→ **may be a precursor for adenocarcinoma of the bladder**

What is an inverted papilloma?

- **BENIGN** proliferative lesion associated with chronic inflammation or BOO
- papillary fronds project into fibrovascular stroma of bladder
- usually covered by thin layer of normal urothelium
- may contain an area of cystitis cystica or squamous metaplasia
- **rare case reports of malignant transformation } especially if glandular type**
→ **more commonly associated with COEXISTENT TCC elsewhere in GU tract or with hx of TCC (high grade) } more so with upper tract TCC than bladder**

What is a nephrogenic adenoma?

- lesion resembling primitive collecting tubule } **single layer of epithelium** (TCC is multi)
- metaplastic response of urothelium to **trauma, infection, or radiation**
- often associated with irritative voiding symptoms
- **BENIGN** but rare cases of transformation to mesonephric adenocarcinoma
- Rx → observation (recurrence common in some so consider cysto)

What is vesical leukoplakia?

- squamous metaplasia with marked keratinization, downward growth of rete pegs (acanthosis), cellular atypia, and dysplasia
- N response of urothelium to noxious stimuli } common in trigone of women
- **may progress to SCC in 20% of patients if keratinizing leukoplakia**

What is pseudosarcoma?

- aka post-operative spindle cell nodule
- rare, **BENIGN** lesion resembling a bladder sarcoma
- reactive proliferation of spindle cells occurring several months after a LUT procedure or UTI
- must r/o leiomyosarcoma

What are the premalignant lesions for each type of bladder cancer?

→ **TCC**

- "CIS"
- atypical hyperplasia (increase in # of cell layers + nuclear abnormalities)
- dysplasia (epithelial changes that are intermediate b/w N urothelium and carcinoma)
- inverted papilloma (glandular type) } likely coexistent

→ **SCC**

- bladder leukoplakia (squamous metaplasia w/ atypia)
- squamous metaplasia with atypia

→ **adenocarcinoma**

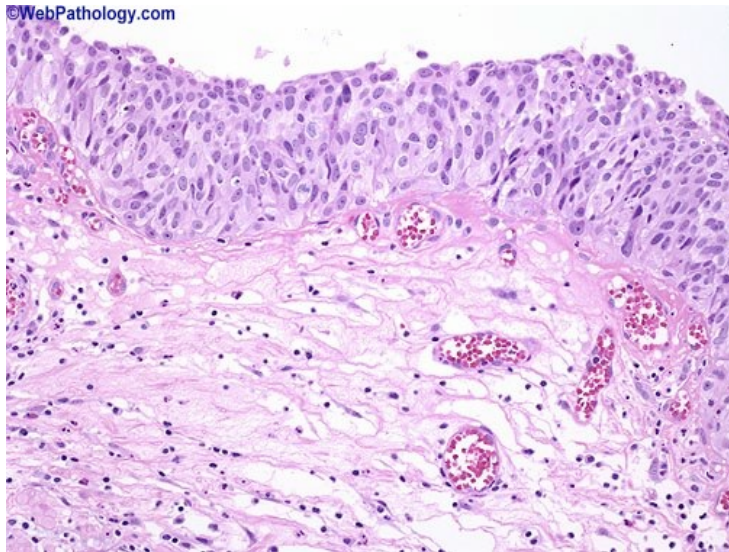
- cystitis glandularis (usually near trigone and assoc'd w/ **chronic UTIs, exstrophy & pelvic lipomatosis**)
- nephrogenic adenoma (rarely degenerates to mesonephric adenocarcinoma)

UROTHELIAL CARCINOMA

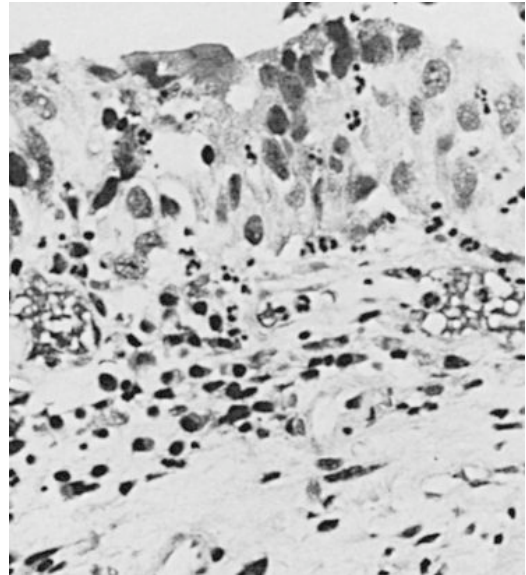
CIS

What is CIS?

- **high grade**, superficial urothelial carcinoma (FLAT)
- often a velvety patch of red } can also be cystoscopically invisible
- **pleomorphic, dark staining, large atypical nuclei** } larger on luminal side
 - **loss of cell polarity + cell denudement + increased nuclear/cytoplasmic ratio**
- may be asymptomatic or may present with severe irritative storage symptoms
- **+ve cytology in 80-90% of CIS patients**
- CIS is present in 25% of patients with high grade, superficial tumours (T1G3)
- **40-80% progress to muscle invasive cancer**
- CIS is present in 20-75% of high grade, muscle-invasive tumours
- **CIS rarely primary disease (1-4%)**
- ~20% with diffuse CIS treated with cystectomy have microscopic muscle-invasive disease



→ CIS of bladder



Urothelial carcinoma (TCC)

What are the features of urothelial carcinoma that are different from normal urothelium?

- **increased # of epithelial cell layers**
- **loss of cell polarity**
- **increased nuclear-cytoplasmic ratio**
- **prominent nucleoli**
- abnormal cell maturation from basal to superficial layers
- clumping of chromatin
- **increased # of mitoses**

What are the patterns of tumour growth seen with urothelial carcinomas?

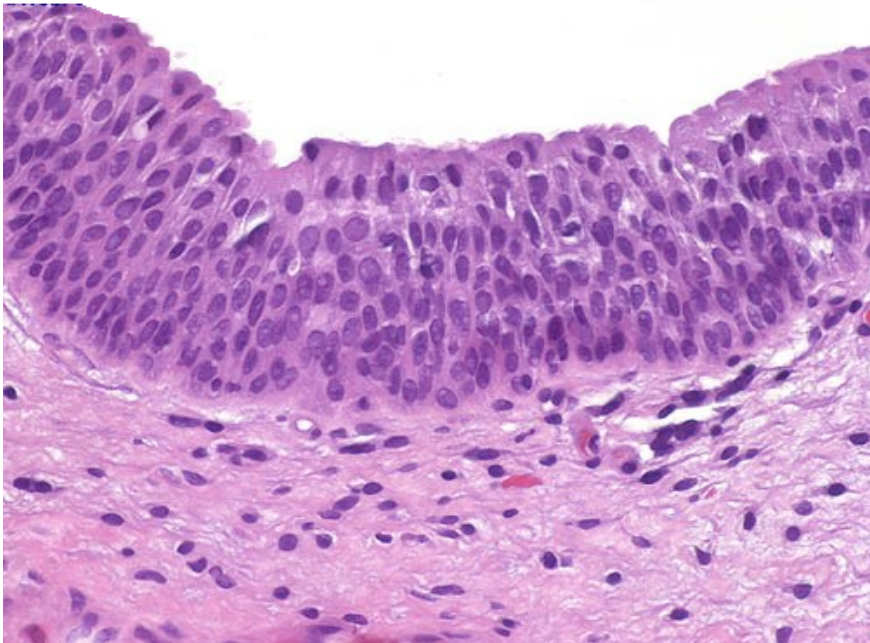
- **papillary (70%)**
- sessile
- infiltrating
- nodular
- mixed
- flat intraepithelial growth (CIS)

What is the grading system of urothelial carcinomas (ISUP)?

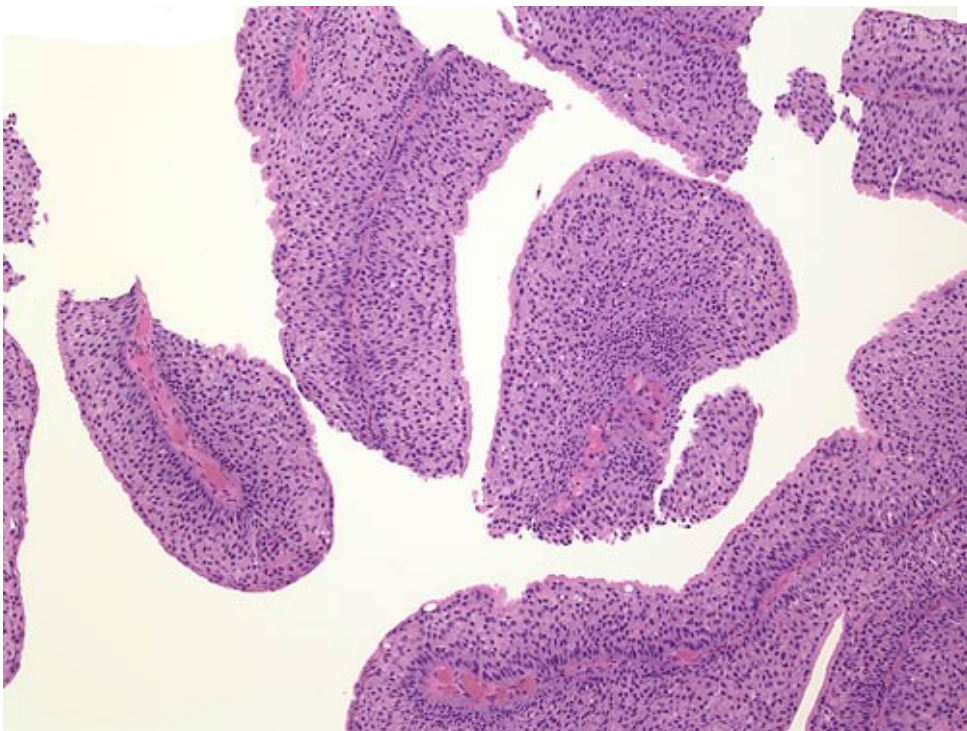
- strong correlation between grade and stage
 - most high grade lesions are muscle-invasive
- **grade correlates with prognosis } stage correlates with survival the strongest**
- many believe low grade tumours have different origins than high grade tumours
 - low grade may be from loss of suppressor genes on chromosome 9q
 - high grade may be from abnormalities in **p53, RB, p16 (suppressor genes)**
- 1) **papilloma** } grade 0
 - } normal urothelium (≤ 7 cell layers thick)
 - } benign but must r/o concomitant TCC → almost never recurs after resection
- 2) well-differentiated } former grade 1
 - } thickened urothelium, only rare mitotic figures, slight anaplasia
 - } mild disturbance of base-to-surface cellular maturation
 - } mild increase in nuclear-cytoplasmic ratio
 - } **PUNLMP when mucosally confined**
- 3) moderately-differentiated } former grade 2
 - } thickened urothelium, a few mitotic figures, slight anaplasia
 - } moderate disturbance of base-to-surface cellular maturation
 - } loss of cell polarity
 - } moderate increase in nuclear-cytoplasmic ratio
 - } **LOW-GRADE** } loss of chromosome 9q suppressor genes
- 4) poorly-differentiated } former grade 3
 - } frequent mitotic figures
 - } no differentiation in base-to-surface maturation
 - } marked nuclear pleomorphism
 - } high nuclear-cytoplasmic ratio
 - } **HIGH-GRADE**
 - **p53, RB, chromosome 9p abnormalities** } found in CIS but NOT Ta

What is the significance of metaplastic elements?

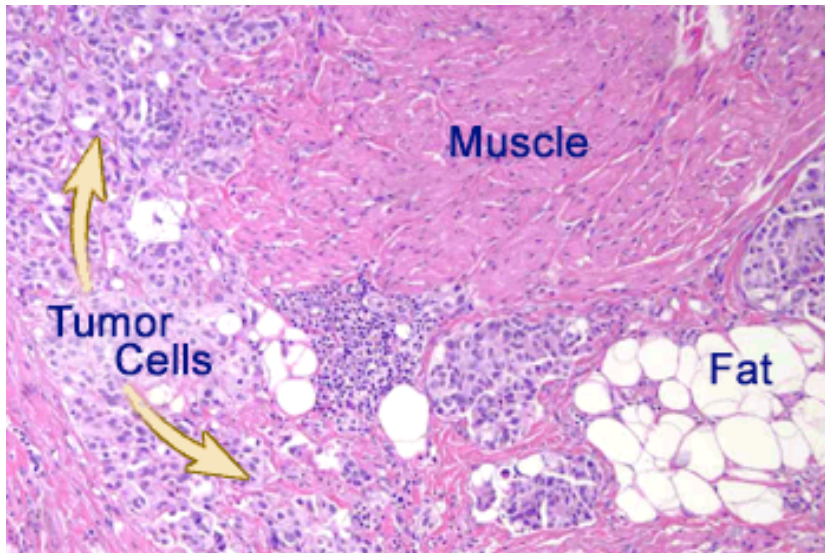
- eg squamous or adenocarcinomatous elements
- presence doesn't change primary classification of tumour as urothelial carcinoma
- found in 30% of muscle-invasive tumours



→ NORMAL UROTHELIUM



→ PAPILLARY UROTHELIAL CARCINOMA



→ MUSCLE INVASIVE UROTHELIAL CARCINOMA

SCC

What is the epidemiology of SCC of the GU tract?

- accounts for ~5% of bladder cancers } much more common in Egypt
→ **bilharzial (*Schistosomiasis haematobium*)**
- usually younger patients
- less male predominance (only 2:1)
- associated with **chronic infection/inflammation**
- cancers are exophytic, nodular, fungating lesions
- **usually low grade**
- low incidence of LN or distant mets } has p53 & chromosome 9 (P16) abN'ities like TCC
- similar prognosis, stage for stage, with TCC
→ **usually poor prognosis b/c of advanced disease at presentation**
- **urine cytology useless**
- **bone is the most common site of mets**

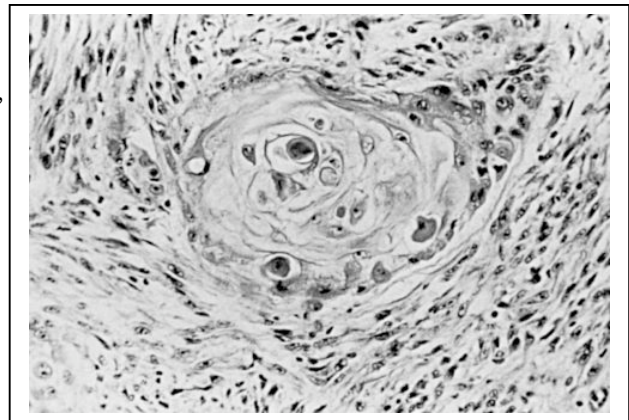
What is the histological findings of SCC?

- **keratinized islands** that contain eccentric aggregates of cells called **squamous pearls**
- grade DOES NOT correlate well with prognosis

What are the RFs for bladder SCC?

- "Some Say Schisto Can Cause Bladder Disease"
- **Smoking**
- **Stones/FBs**
- **Schistosomiasis haematobium**
- **Chronic UTIs**
- **Chronic indwelling catheter**
- **BCG**
- **Diverticula (bladder)**

?cyclophosphamide



→ BLADDER SCC (squamous pearls)

Adenocarcinoma

What is the epidemiology of adenocarcinoma of the GU tract?

- account for <2% of primary bladder cancers
- can also occur in intestinal conduits, augments, pouches, etc
- **majority represent mets from GI tract, breast, lung } r/o colon primary**
- usually arise in trigone or in dome (urachal)
- **most common type of bladder Ca in exstrophy & associated w/ pelvic lipomatosis**
 - develop in response to chronic inflammation and irritation
- most are poorly differentiated and invasive
- **more often associated with cystitis glandularis than CIS**
- generally poor prognosis due to advanced stage at presentation
 - stage for stage, similar to TCC

What are the RFs for adenocarcinoma of the bladder? }} “UCC CUBE”

- Urachal cyst/remnant
- Cystitis glandularis
- CIS
- Chronic inflammation
- Ureterosigmoidostomy
- Bladder augment
- Exstrophy of bladder

What are the classifications of adenocarcinomas of the GU tract?

- 1) primary vesical
- 2) urachal
- 3) metastatic

What are urachal carcinomas?

- very rare tumours arising outside the bladder
 - **usually adenocarcinomas** but can also be TCC, SCC, or even sarcomas
 - sharply demarcated from normal bladder epithelium } tumour is found in bladder wall
 - may present with bloody or mucoid discharge from umbilicus
 - if tumour invades bladder may present with mucosuria
 - may present as palpable mass after forming mucocele
 - **often have stippled calcifications on xray**
 - **POOR PROGNOSIS } worse than primary bladder adenocarcinoma**
 - **histologically invades deeper and wider than expected**
 - often compromises results of partial cystectomy
 - mets to iliac & inguinal LNs, omentum, liver, lung, bone
- Rx → partial cystectomy + resection of entire urachus

How common are metastatic adenocarcinomas of the bladder?

- most common form of adenocarcinoma of bladder
- primary sites include rectum, stomach, endometrium, breast, prostate, and ovary

ORIGINS AND PATTERNS OF DISSEMINATION

What are the main patterns of spread of urothelial carcinoma?

- 1) direct extension } involves
 - a) angiogenesis
 - fibroblast growth factors (FGF) & VEGF
 - b) proteolysis of basal lamina
 - collagenase type 4 (an MMP; inhibited by TIMPs)
 - urokinase plasminogen activator (u-PA)
 - c) increased cellular motility
 - reduction of adhesion molecules such as E-cadherin
 - d) proliferation
 - increased EGF receptor expression
 - e) escape from local surveillance mechanisms (immune system)
- 2) metastatic spread } ~5% of all low-grade superficial disease will progress to mets
 } ~20% of high-grade disease (including CIS) will progress to mets
 } **mets rare without muscle-invasion**
- 3) lymphatic spread } extent of primary + LN status affects survival after surgical excision
 } **obturator (75%) & pelvic (65%) LNs most common**, presacral (~25%)
 → paravesical (15%) is worst prognosis
- 4) vascular spread } 5yr survival in patients with distant mets is very low
- 5) implantation } can spread into abdo wounds, denuded urothelium, resected prostatic fossa,
 or traumatized urethra
 } occurs most commonly with high-grade tumours

What are the 2 main theories on the origins of urothelial carcinoma?

- 1) field change disease
- 2) original lesion + clonal seeding (recurrences)

What are the 3 main mechanisms of local invasion?

- en bloc spread (invading broad front) → 60%
- tentacle-like invasion → 25%
- lateral spread → only 10%

How common is prostate involvement in muscle-invasive disease?

- ~40% of cystectomy patients
- prostatic urethra is usually site of involvement
 - 40% have concomitant stromal invasion
 - ~6% have prostatic stromal involvement WITHOUT prostatic urethral involvement
- **presence of prostatic stromal invasion also predictive of subsequent distant mets → 80%**

What are the common sites of distant bladder metastasis? }} “LL BAG”

- Liver (40%)
- Lung (35%)
- Bone (27%) } much more common with bilharzial SCC of bladder
- Adrenals (20%)
- GI tract (15%)

NATURAL HISTORY

What is the natural history of urothelial carcinomas of the bladder?

- **~75% present with superficial disease**
 - ~55-60% present with low grade Ta tumours
 - most develop recurrences } ~20% recur with high grade disease
 - ~5% progress onto $\geq T2$ disease
 - most young patients (<30yrs) present with TaG1
 - ~20% present with high grade superficial tumours
 - 30-50% with T1G3 will progress on to $\geq T2$ disease
- **~25% present with $\geq T2$ disease**
 - almost 50% have occult distant mets } clinical mets seen within 1yr in most
- **2% has upper tract disease at initial presentation**

PROGNOSTIC INDICATORS

What are the RFs for recurrence or progression of superficial disease?

- **grade } #1 RF for progression**
- **stage**
- **presence of CIS**
- **multifocality } #1 RF for recurrence**
- cysto at 3months post-TURBT
- interval between prior recurrence
- lymphatic invasion
- tumour size (>3cm)
- papillary vs solid
- presence of nested variant (micropapillary variant) } very bad
- **p53 status**

What other prognostic indicators are being researched?

- predicting poor outcomes
 - **+ve Ki67 staining → bad prognosis**
 - **chromosome 17p deletions (p53) → progression**
 - **p53 nuclear accumulation → invasive (most promising)**
 - **reduced E-cadherin levels → invasive**
 - **elevated EGF receptors → invasive**
 - **amplification of HER2/Neu oncogene → progression**
 - **chromosome 9 deletions → recurrence and BCG failure**
 - elevated hyaluronidase activity → high grade disease
 - high urine fibronectin → invasive and predicts poor BCG response
- predicting better outcomes
 - **chromosome 9q deletions → superficial disease**
 - heterogeneous staining of EMA → better survival
 - elevated TGF- β expression in tumour → less aggressive
- Lewis x blood group antigen → bladder cancer

What are the markers of proliferation?

- nondiploid fractions
 - increased DNA-synthesizing S phase fraction
 - increased PCNA
- \ } higher percentage of proliferating cells
/ correlates with aggressiveness

What are the markers of apoptosis?

- survivin levels → inhibits apoptosis and so is upregulated in many cancer

DIAGNOSIS

How does bladder cancer present?

- **painless hematuria** → **most common symptom (found in 85%)**
- irritative symptoms (frequency, urgency, dysuria) → 2nd most common symptom
→ associated with CIS or invasive TCC
- flank pain } ureteral obstruction
- lower limb edema
- pelvic mass
- abdo pain, bone pain
- constitutional symptoms

What are the AUA guidelines on microscopic hematuria?

→ **microscopic hematuria = ≥ 3 RBC/hpf from a fresh MSU on 2 of 3 samples**

- 1) high-risk patient
 - microscopic hematuria x1 warrants FULL UROLOGIC EVALUATION
 - a) hx and P/E
 - b) urine cytology
 - c) upper tract imaging
 - d) cystoscopy
 - high risk includes:
 - smoking hx
 - hx of gross hematuria
 - hx of urologic dz
 - hx of UTI
 - hx of pelvic RADs
 - occupational exposure
 - age >40yrs
 - hx of irritative symptoms
 - analgesic abuse
- 2) low-risk patient
 - if suggestion of benign cause (UTI, intercourse, menstruation, vigorous exercise)
then REPEAT U/A 48hrs AFTER CESSATION OF ACTIVITY
 - otherwise:
 - a) UPPER TRACT IMAGING
 - b) URINE CYTOLOGY
- 3) presence of significant proteinuria (>1g/day), RBC casts, or renal insufficiency warrants REFERRAL TO NEPHROLOGIST
- 4) if -ve evaluation, repeat U/A, URINE CYTOLOGY, and BP check at 6, 12, 24, 36 months

What are the CUA guidelines (2008) on microscopic hematuria?

→ **microscopic hematuria = ≥ 3 RBC/hpf on 2 u/a**

→ if urinalysis performed after recent exercise, menses, intercourse, etc should REPEAT AFTER STOPPING ACTIVITY and if negative, no further work-up required

- 1) presence of proteinuria, RBC casts, or dysmorphic red cells +/- elevated serum Creat warrants REFERRAL TO NEPHROLOGIST
- 2) ALL PATIENTS SHOULD GET MINIMAL WORK-UP
 - a) urine cytology
 - b) upper tract imaging } U/S is 1st line
- 3) >40yrs old, +ve or atypical urine cytology, or +RFs (SOLAR-C)
 - RFs include smoking, occupational exposure, irritative LUTS, analgesic abuse, pelvic RADs, cyclophosphamide exposure
 - SHOULD GET CYSTO
- 4) <40yrs old, N cytology, no RFs
 - repeat urinalysis + urine cytology + BP checks at 6, 12, 24, 36 months
 - no f/u required after 3yrs of N tests
 - reassessment ONLY if gross hematuria, +ve or atypical cytology, or irritative LUTS

What is the role of urine cytology?

→ **high specificity (low false positives)**

- usually positive only with high-grade disease and CIS
→ can have ~20% false negative rate
- cancer cells are more cohesive in well-differentiated, low grade disease
→ cells are not shed in urine
- **can see 1-10% false positive rate**
→ from urothelial atypia, cystitis glandularis, inflammation, or changes due to RADs or chemo
- **urine cytology NOT A GOOD SCREENING TOOL } poor sensitivity (>20% false -ves)**
- **+ve cytology in face of TaG1 tumour may mean concomitant CIS somewhere else**

Are washings better than voided cytology?

- washing gives more surface epithelial cells so may be better
- if flexible scope used however, this difference may be negated because far less epithelial cells
- **washings ideal for sampling upper tracts and prostate**

What is the value of flow cytometry?

→ **overall, no added benefit over cytology**

- can measure DNA content only in cells staining +ve for cytokeratins (epithelial)
- diploid tumours } low grade and low stage, better prognosis
- triploid to tetraploid tumours } poor prognosis

What is the value of image analysis?

→ analyzes DNA content in each cell & identifies cells with abN amounts of DNA via fluorescence pattern

EARLY DETECTION

What are the biases involved in the attempt to determine whether screening is beneficial?

- lead time bias } earlier diagnosis but no change in mortality
- length time bias } tendency to diagnose more indolent tumours with longer preclinical durations
- selection bias } tendency for participants in early detection programs to be more healthy & health conscious

Is there any evidence for bladder cancer screening?

→ **YES eg Messing et al (Wisconsin trial)**

- home dipstick screening for hematuria
 - screened and unscreened had similar proportions of low grade (55%) and high grade (45%)
 - low grade were almost all T1 or less in both groups
 - 50% of high grade in unscreened were muscle invasive
 - 10% of high grade in screened were muscle invasive
 - mortality was significantly reduced in screened group
- \ } decreased risk of muscle invasive
/ disease and mortality

What is the argument against using cytology, flow cytometry, imaging analysis, and marker tests to screen for bladder cancer?

- not sensitive for small tumours } would miss 10-20% of high grade tumours
- poor sensitivities for low grade tumours
- would miss significant amount of tumours, even though most of those would be superficial
- cost

What screening tools for bladder are being researched?

- Lewis x blood group antigen
 - antigen M344
 - DD23 antigen
 - Hyaluronic acid (HA) or hyaluronidase in urine
 - **BLCA4 protein in urine**
 - **NMP22 protein in urine (more sensitive than cytology)**
 - telomerase RNA in urine
 - **microsatellite nucleotide repeat analyses**
 - survivin protein in urine
 - **DNA FISH (highest specificity)**
- NOT adequate to replace cysto for evaluation of hematuria
- may be useful in replacing some surveillance cystoscopies in monitoring low risk superficial bladder cancer but likely are NOT satisfactory for screening
- may have promise in high risk groups eg aluminum or benzidine workers

What are the important points to remember during the initial TURBT?

- fulguration or laser ablation of suspicious lesions w/o Bx is NOT ADEQUATE in initial evaluation of a bladder tumour
- try to send separate specimens
 - a) bulk of tumour
 - b) deep base + underlying muscle
- if unable to resect fully, obtain enough to make accurate histologic diagnosis
- resect without regard for the orifice, but don't fulgurate
 - +/- stent
- paralysis necessary for lateral wall tumours to prevent obturator reflex
- tumours in bladder tics should be sampled rather than resected

What are the indications for random bladder Bx's?

- 1) partial cystectomy (or diverticulectomy) is planned
- 2) +ve cytology with no visible tumours, only papillary lesions (Ta), or low grade TCC on path
- 3) ?? consideration of orthotopic neobladder } prostatic urethral Bx
 → systematic Bx's best } dome, left lateral, right lateral, trigone, prostatic urethra

STAGING

What is the accuracy of staging bladder TCC?

- ~30% understaged
- ~10% overstaged

What is the recommended staging workup for bladder cancer?

- 1) primary TURBT
- 2) bimanual exam during TURBT
 - if palpable before resection, likely deep T2 or more
- 3) for superficial disease
 - no further imaging recommended } consider upper tract imaging
- 4) for muscle-invasive disease
 - CBC, lytes, creatinine, LFTs and ALP
 - CXR
 - biphasic CT urogram } better if done before TURBT
 - } can only assess large LNs and large liver mets
 - bone scan
 - MRI } not significantly better than CT
 - } better in detecting bone mets than CT and bone scans

What is the role of fluorescent cystoscopy using **intravesical 5-ALA** (aminolevulinic acid)?

- can see tumours not seen by white light } uses blue light (375-440nm) → **high sensitivity**
- reduces recurrence rates and may prevent disease progression
- problem is that it has **low specificity** (high false negatives)

What is the role of PET scans for bladder cancer?

- **not good for staging** because FDG reagent excreted in urine
- **helps assess masses that are possible mets or possible local recurrences post-cystectomy**
→ helps guide the need for Bx

What are the main regions of lymphatic drainage from the bladder?

- internal iliac
- obturator (most commonly involved)
- external iliac
- presacral
- perivesical (less involved than others)

What are the boundaries of the STANDARD staging lymphadenectomy?

- slightly above bifurcation of iliacs
- down to femoral canals
- lateral to genitofemoral nerves
- medial to bladder pedicles

How common is mets to the LNs?

- close to zero in low grade, superficial
- **5-10% in T1G3 disease**
- **40% in T2 disease**

What is the 1997 AJCC TNM staging of bladder cancer?

- T } Ta – papillary
Tis – flat CIS
T1 – lamina propria invasion
T2a – superficial muscularis propria invasion
T2b – deep muscularis propria invasion
T3a – microscopic extension into perivesical fat
T3b – macroscopic extension into perivesical fat
T4a – invading pelvic viscera (eg prostatic stroma, vaginal wall, rectum, uterus)
→ not fixed
T4b – invading pelvic side wall, abdo wall, bony pelvis
→ fixed
- N } No – no pelvic node mets
N1 – single node ≤ 2 cm below common iliacs
N2 – single node 2-5cm or multiple small nodes (< 5 cm)
N3 – node > 5 cm
- M } Mo – no distant mets
M1 – distant mets

PREVENTION

What has been suggested for chemoprevention of bladder cancer?

- studied as secondary prevention as well as primary prevention in high-risk groups
- vitamins } vitamin A, B6, E, Zn, Se
- polyamine synthesis inhibitors } DFMO (difluoromethylornithine)
- COX inhibitors
- dietary alteration } urinary acidification, soy, green tea extract, high fluid intake, low-fat diet
- **no consistent significant benefits seen**
- **STOP SMOKING ... PROVEN PREVENTION**

NON-UROTHELIAL TUMOURS OF THE BLADDER

What is small cell carcinoma of the bladder?

- **derived from neuroendocrine stem cells or dendritic cells**
 - **stain +ve for enolase**
- may be mixed with elements of TCC
- very aggressive with early vascular and muscle invasion
- should also be evaluated for small cell carcinoma of lung or prostate which may have metastasized to the bladder
- Rx } requires multi-modal therapy → chemo + surgery/rads**
 - chemo recommended first even if tumour seems confined (cisplatin-based)
 - poor prognosis } only 65% cured after chemo + Sx even if localized
 - 40% for chemo + Rads

What is carcinosarcoma of the bladder?

- **rare, highly malignant tumour containing malignant mesenchymal & epithelial elements**
 - mesenchymal elements } chondrosarcoma or osteosarcoma
 - epithelial elements } TCC, SCC, or adenocarcinoma
- usually in middle-aged men
- poor prognosis
- should not be confused with urothelial cancers with prominent spindle cell component
- Rx } multimodal therapy → GC chemo + surgery +/- RADs**

What are the most common primaries in metastatic bladder cancer?

- | | |
|------------------|----------------------|
| - prostate | - breast |
| - ovary | - kidney |
| - endometrial | - stomach |
| - colon & rectal | - melanoma |
| - lung | - lymphoma, leukemia |

What is signet cell carcinoma?

- rare variant of adenocarcinoma } 2/3 originate in bladder and 1/3 from urachus

NON-EPITHELIAL BLADDER TUMOURS

What are the common non-epithelial bladder tumours?

→ **5% of all bladder tumours**

1) sarcoma (most respond poorly to chemo and Rads)

a) angiosarcoma and hemangioma → bladder hemangiomas are rare

- can get malignant degeneration (rare)

→ angiosarcomas are very rare

- 20% come from previous hemangiomas

→ mets rapidly to hematogenous sites

Rx } laser or TUR of hemangiomas (can recur)

} partial cystectomy

b) leiomyosarcoma → **MOST COMMON mesenchymal bladder tumour**

- also the most common sarcoma in kidney

→ 2x more common in M

→ appears as submucosal nodule or ulcerating mass

→ r/o benign leiomyoma

→ poor survival (5yr disease specific is 62%)

Rx } aggressive surgical extirpation

c) rhabdomyosarcoma → most common in **young kids**

→ embryonal type in kids (favorable histology – spindle or botryoid)

→ spindle cell, alveolar cell (bad histology), or giant cell type in adults

→ poor prognosis and don't respond well to chemo or rads

Rx } aggressive surgical extirpation in adults

} CHEMO + RADs + surgery

d) other → liposarcomas, chondrosarcomas, osteosarcomas are very rare

Rx } aggressive surgical extirpation

2) primary bladder lymphoma → arises from submucosal lymphoid follicles

→ **2nd most common non-epithelial bladder tumour**

→ more common in women, usually in 40's to 60's

Rx } CHEMO + RADs, partial or radical cystectomy

3) neurofibroma → benign Schwann cell tumour (stains for S-100 protein & type 4 collagen)

→ may be part of AD neurofibromatosis with variable penetrance

→ usually seen in kids or young adults

→ can rarely undergo malignant change into neurofibrosarcoma

4) pheochromocytoma → usually from paraganglionic cells in bladder wall near trigone

→ usually seen during teens to 30's

→ syncope on filling/emptying of bladder in 67% } hormonally active

→ 10% are malignant

Rx } partial cystectomy → TURBT contraindicated (HTN'sive crisis)

5) plasmacytoma, granular cell myoblastoma, malignant melanoma, choriocarcinoma, and

yolk sac tumours → same behaviour as their counterparts in other body sites

Rx } same as counterparts in other sites of body

Chapter #76 – Non-Muscle Invasive Bladder Ca

What percentage of patients with hematuria have bladder cancer?

- microscopic } 1-10%
- gross } 15-35%
- presence of irritative symptoms may double risk, esp for CIS (5% vs 10%)

What is the stage at presentation of bladder tumours?

- **70-75% are non-muscle invasive**
 - 70% Ta
 - 20% T1
 - 10% CIS
- ~25-30% are muscle-invasive
- ~30% of patients with “non-invasive” disease actually have T2 or greater } understaging
- that means ~40% have invasive disease at Dx } although there is ~10% overstaging

What are the chances of progression & death based on tumour type (CHART)?

- Noninvasive
 - papilloma } <1%
 - PUNLMP } 3%
 - TaG1 } **5-10%** → <5% death
 - TaG3 } 15-40% → 10-25% death
- Invasive
 - T1G3 } **30-50%** → 33% death
- CIS
 - primary } **>50%**

*** **high grade lesions progressed at almost same rates, despite Ta or T1 pathology** ***

STAGING

What is the new WHO grading of urothelial carcinoma?

- PUNLMP
- low grade (old grade 1 and 2) } well and moderately differentiated
- high grade (old grade 3) } poorly differentiated

What are the 3 main layers of the bladder?

- 1) urothelium
- 2) lamina propria
- 3) muscularis propria (detrusor)

What are the main prognostic indicators for bladder cancer progression?

- **grade*****
- **stage**
- **presence of CIS**
- tumour size (>3cm)
- multifocality (#1 RF for recurrence)
- sessile vs papillary
- presence of LVI
- recurrence at 3 month cysto post-TURBT

*** **MOST IMPORTANT RISK FACTOR FOR PROGRESSION IS GRADE NOT STAGE** ***

Which chromosomal abnormalities are associated with bladder urothelial Ca?

1) low grade

- relatively few chromosomal abnormalities
- chromosome **9q**

2) high grade

- tend to have numerous chromosomal gains and deletions
- RAS p21 oncogene
- **p53 gene** (chromosome 17p)
- **RB gene** (chromosome 13q)
- chromosome 7
- chromosome 9

Stage for stage, how common is high-grade disease?

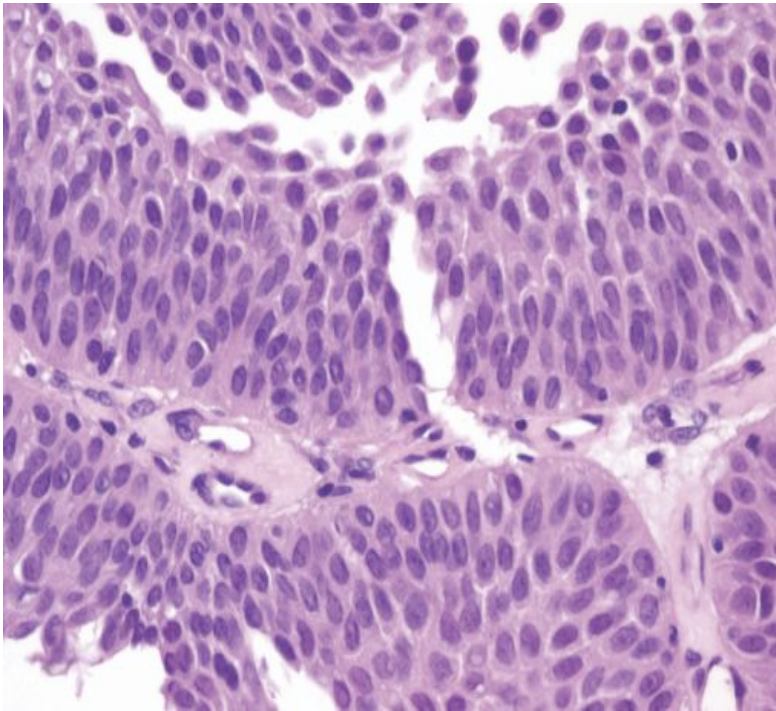
- Ta } about 7% are high grade
→ should be considered high risk
- T1 } 10-30% are high grade
→ T1G3 has almost 50/50 chance of progressing to muscle-invasive disease
- CIS } 100% high grade

How common is recurrence & progression based on stage & grade?

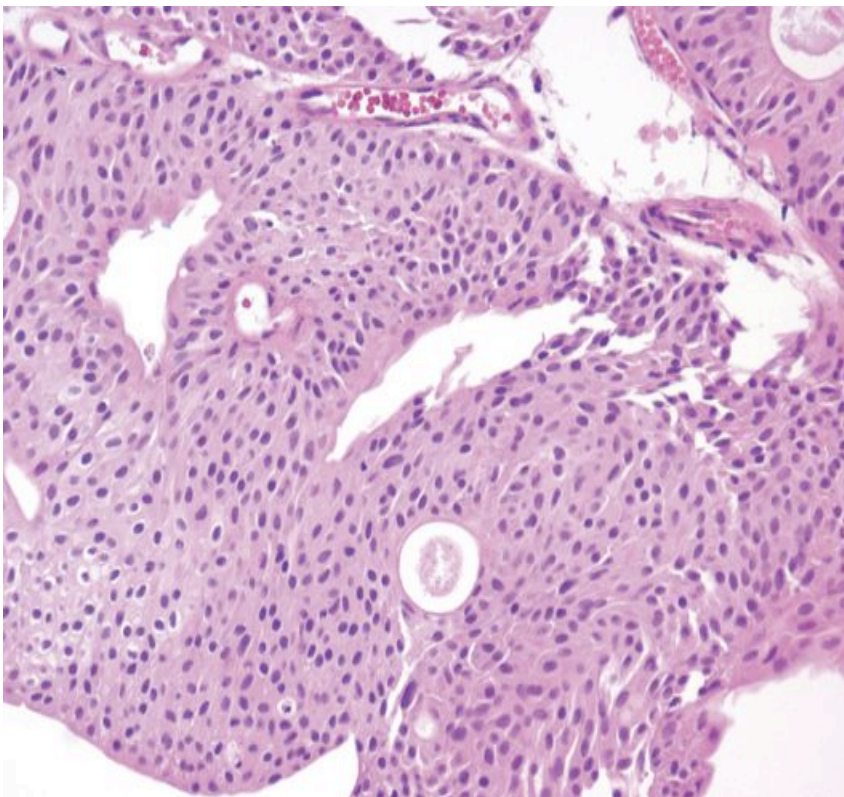
Tumour	recurrence rate	progression rate
Low grade Ta	50-70%	~5%
High grade Ta		15-40%
Low grade T1	>80%	
High grade T1		30-50%
CIS (primary)		>50%

What is the significance of CIS?

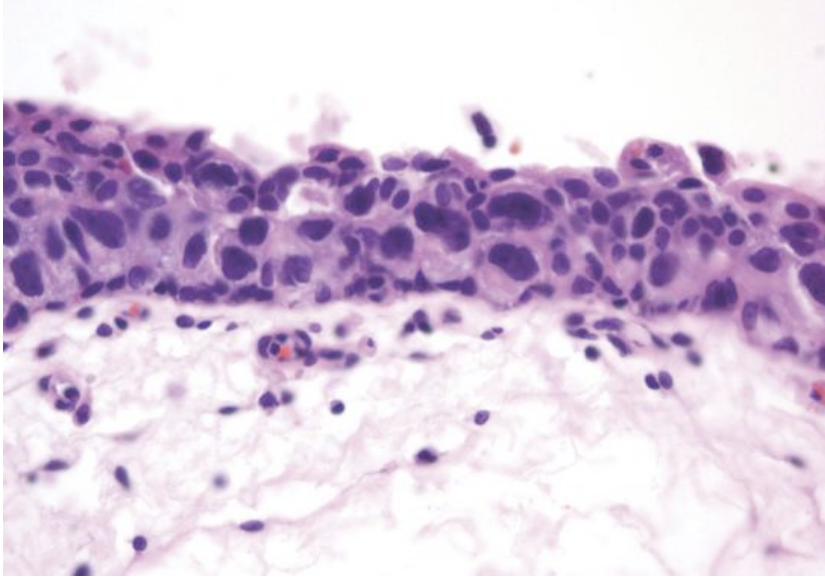
- not “pre-malignant” } flat, noninvasive urothelial carcinoma
→ **should be considered “pre-invasive” high grade TCC**
- **40-80% progress to muscle invasive cancer**
- ~20% of those thought to have CIS only have ≥T2 disease after cystectomy
- important prognostic factor } some say 2nd most after grade (Millan-Rodriguez '00)



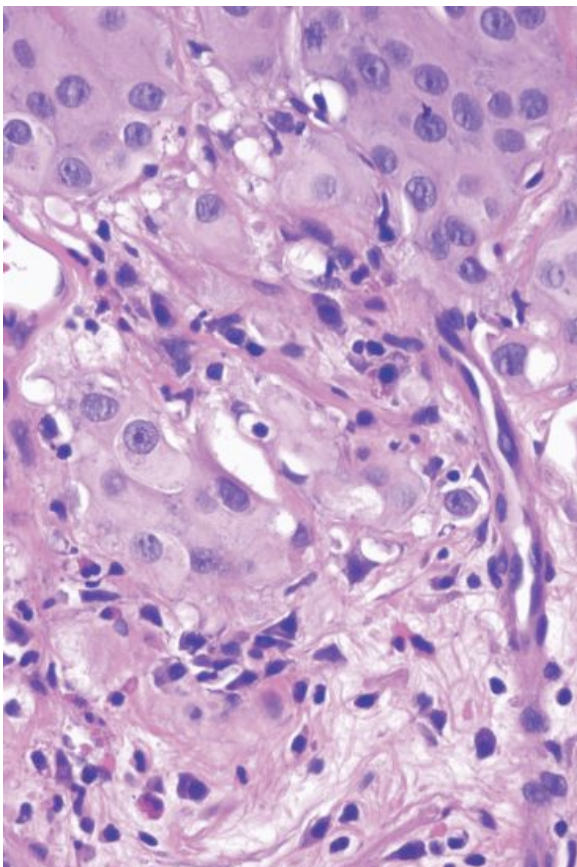
→ PUNLMP



→ LOW GRADE Ta UROTHELIAL CANCER (TaG1)



→ CIS of BLADDER



→ HIGH GRADE T1 UROTHELIAL CANCER (old T1G3)

ENDOSCOPIC SURGICAL MANAGEMENT

Why is NS not used during TURBT?

- NS conducts electricity and disperses energy from cutting loop
- glycine or sterile water preferred } glycine more expensive

What are the benefits of bipolar TURBT?

- bipolar loop allows resection in NS
- less risk of obturator reflex

What is the management of diverticular tumours?

- careful resection + fulguration of base } try to resect near neck & avoid deeper area
→ if high grade, repeat TURBT and include perivesical fat (small perforation inevitable)
- indwelling Foley allows healing
- partial or radical cystectomy for high-grade diverticular tumours recommended
→ need to do random bladder biopsies if partial cystectomy/diverticulectomy

What are the indications for a temporary PU prior to TURBT?

- obese patient and unable to reach tumour
- urethral length too long
- urethral stricture
- penile prosthesis
- unable to position patient

What are the potential complications of TURBT?

- 1) intra-op } severe bleeding (<5%)
 } perforation (<5%)
 } obturator reflex
 } urethral false passages/trauma
 } TUR syndrome
 } sepsis
- 2) post-op } delayed bleeding +/- clot retention
 } seeding from perforation (very low)
 } irritative voiding symptoms
 } infection
 } urethral strictures
 } ureteral orifice scarring/obstruction
 } foot drop (common peroneal nerve)

What methods are used to avoid the obturator nerve reflex?

- GA + muscle relaxant
- bipolar cautery loop to minimize conduction
- spinal anesthesia (obturator block) to minimize adductor muscle spasm
- laser fulguration
- avoid overfilling bladder

What is TUR syndrome?

- due to absorption of irrigant fluid } rare with TURBT
- manifests as confusion, N/V, HTN, bradycardia, visual disturbances
- can get dilutional hyponatremia, hypervolemia, hypo-osmolality of serum & renal dysfunction from glycine toxicity
- can get hyperammonemia from glycine absorption
- up to 20cc per minute absorption (1.2L per hr)

What are the indications for repeat TURBT?

→ usually 2-4 weeks after first resection

1) incomplete tumour resection

- large tumour
- anatomic inaccessibility
- medical instability
- perforation

2) all T1 disease (esp T1G3)

- 20-30% will have T2 disease if muscle present on first TURBT
- 40-60% will have T2 disease if no muscle on first TURBT

3) for 2nd opinion when there is questionable muscle-invasion on first TURBT

4) TaG₃

- controversial but most would recommend re-TURBT

5) muscle invasive disease prior to bladder conservation therapy

What are the proposed benefits of re-TURBT for T1 disease?

- 1) remove residual tumour } present in 40-50%
- 2) identifies understaging } 25-50%
- 3) provides prognostic info } $\leq T1$ residual = ~15% progression
 } residual T1 = 75% progression
- 4) improves results of intravesical therapy } decreased recurrence & progression rates

What are the indications for random bladder Bx's?

- 1) partial cystectomy (or diverticulectomy) is planned
 - 2) +ve cytology with no visible tumours
 - 3) +ve cytology with only papillary lesions (Ta) or low grade TCC on path
- *** consideration of orthotopic neobladder } prostatic urethral Bx ***

What are the arguments against random bladder biopsy?

- denudation of urothelium with risk of implantation
- increased risk of bleeding
- increased risk of perforation

Is it safe to perform TURP with TURBT?

- safe with low grade tumours } **avoid if suspicious for high-grade tumours**

What is the rationale for peri-op intravesical therapy?

- kill non-visualized tumour cells
- prevent implantation
- decrease recurrence rates

What is the best peri-op intravesical chemotherapeutic agent?

- mitomycin C (MMC) } 40mg in 40cc NS
 - best if given within 6 hrs (MMC is good for ~1week at room temp)
 - leave in bladder for 1hr
 - no benefit of further doses after single post-op dose
- **MMC decreases recurrence rates by ~50% } no effect on progression**

What are the indications for post-op intravesical chemotherapy?

- 1) multiple tumours
- 2) recurrent tumour
- 3) tumour suspicious for high grade (including CIS)
- 4) hx of T1 bladder tumours
- 5) ? first presentation of bladder lesion } AUA Guidelines say option, but not standard or recommendation

What are the contraindications of post-op intravesical chemotherapy?

- bladder perforation

Why can't BCG be given post-TURBT?

- high risk of bacterial sepsis and death

What are the benefits of laser fulguration of bladder tumours?

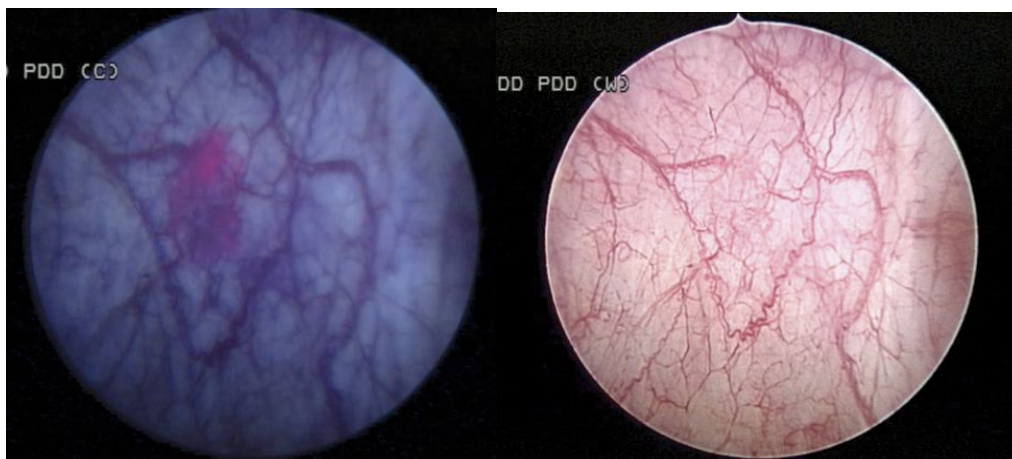
- for recurrent low grade lesions with known biology
- Nd:YAG laser best
- less risk of bleeding
- no risk of obturator reflex
- can be done under intravesical anesthesia for small lesions
- ? lower recurrence rates
- draw back is NO PATHOLOGY and cost

What is the main complication of laser fulguration?

- forward scatter of laser energy to adjacent structures } rare
- can result in perforation of hollow viscous organs eg bowel

What is the role of fluorescent cystoscopy?

- intravesical 5-ALA derivatives (eg HAL) can improve tumour detection
 - accumulates in neoplastic cells } looks red under blue light
- identifies both papillary & CIS
- high sensitivity BUT low specificity (high false +ves)



→ 5-ALA BLUE LIGHT FLUORESCENT CYSTOSCOPY

IMMUNOTHERAPY

How does intravesical therapy work against urothelial carcinoma?

- instillation results in massive local immune response characterized by expression of **cytokines** in the urine and bladder wall with an **influx of granulocytes & mononuclear cells**
- **initial step is a direct binding to fibronectin within the bladder wall**
- binding leads to initiation and maintenance of inflammatory processes
 - TNF- α → GM-CSF
 - IFN- γ → IL-2
- **cytokine induction (esp IFN- γ and IL-2) leads to induction of Th1 response**
 - leads to cell-mediated cytotoxic mechanisms

BCG

What is BCG?

- bacillus Calmette-Guerin
- **live attenuated mycobacterium (*M. bovis*)** initially developed as a vaccine for TB
- initial regime involved im dose + intravesical regime (Morales et al '85)
- initially discovered because patients with TB and lung Ca had regression of their lung tumours
- mechanism of action is not clear } upregulation of cytokines and TH1 response
- **higher efficacy against CIS and recurrence than intravesical chemo, but worse s/e's**

How should BCG be administered?

- stored in refrigeration and reconstituted from a powder
- 81mg (10 million organisms) mixed in 50cc NS & administered via catheter } left in for 2hrs
- amount of bacterium given for intravesical Rx is $\sim 10^6$ greater than percutaneous vaccine dose
- treatments begun few wks after TURBT to allow re-epithelialization of urothelium

What are the indications for BCG therapy?

- 1) T1 disease, any grade
- 2) high grade disease
- 3) multiple diffuse Ta disease
- 4) large tumour >2cm
- 5) primary treatment of CIS
- 6) recurrence within 1 yr
- 7) maintenance therapy
- 8)* +ve urine cytology after resection of all visible tumour

What is the role for BCG in CIS of the bladder?

- **recommended by the AUA guidelines as the preferred initial treatment of CIS**
- initial tumour-free response rate is as high as 80%
- $\sim 50\%$ have a durable response for a median period of 4 yrs
- over 10yrs, only 30% remain progression or recurrence free } close f/u required
 - most recurrences or progression occurs within first 5 yrs
- progression in responders is $\sim 20\%$ but in non-responders it is 95%

What is the role for BCG for treatment of residual tumour?

- can treat residual papillary tumours } **60% response rate**
- also used for carcinoma of mucosa or superficial ducts of the prostate } 50% tumour-free rate
- **DOES NOT SUBSTITUTE FOR SURGICAL RESECTION**

What is the role of adjuvant BCG for prevention of recurrence?

- **shown in several large series to decrease recurrence post-TURBT by ~40%**
- role especially for high-risk patients
 - } high grade
 - } T1
 - } CIS
- **NOT RECOMMENDED FOR LOW-RISK DISEASE DUE TO S/E PROFILE**

What is the role of adjuvant BCG in preventing progression?

- several studies have shown a delay in progression with adjuvant BCG therapy
 - **Sylvester et al '02** → meta-analysis of non-muscle invasive disease (Ta, T1, CIS)
 - BCG reduced risk of progression at 2.5yrs by 27% (9.8% vs 13.8%)
 - benefits only seen in trials using BCG maintenance
 - risk of progression in CIS pts was reduced by 35% in BCG group vs intravesical chemotherapy group
 - no significant difference in deaths
 - short f/u (only 2.5yrs)
 - only 25% of patients finished entire BCG maintenance regime
 - **Herr et al '88** → randomized trial of 86 pts w/ high-risk superficial disease (BCG vs TUR alone)
 - greater delay in interval progression for BCG patients
 - cystectomy rate for CIS was lower in BCG group (11% vs 55%)
 - but only 27% of patients were alive with bladder at 10-15yr f/u
- BCG is only agent shown to delay or reduce high-grade tumour progression**

What is the optimal treatment schedule and dose for BCG?

- schedule
 - Morales et al used 6 wk induction } Frappier labs sent packs of 6 vials
 - Bohle et al also found 6 wk induction to be ideal for maximum response to BCG
 - avg additional response from 2nd induction course is 25-30%
 - additional courses, for refractory patients, after 2nd induction course are associated with a significant risk of tumour progression in 20-50% (Nadler et al '94)
 - response to BCG at 6mos can be used as predictor of progression (Orsola et al '98)
 - dose
 - decrease in toxicity w/ no statistical difference in efficacy was noted in some series
 - multifocal & high-grade tumours may respond better to full dosing
- ➔ OPTIMAL SCHEDULE & DOSE UNDETERMINED, BUT AT LEAST 1 YR OF MAINTENANCE BCG IS SUGGESTED**

What is the role of maintenance BCG?

- **SWOG trial (Lamm et al '00)**
 - 6 wk induction then 3week maintenance at 3 and 6 months then q6months for 3yrs
 - median recurrence-free survival better for maintenance arm (76.8 vs 35.7months)
 - overall 5yr survival was better in maintenance arm (83% vs 78%)
 - **only 16% tolerated entire schedule** } benefits despite failure to get full Rx
 - } maybe don't need full 3yrs (fall-off at 1yr)
- maintenance therapy may be given at 1/3 dose with similar efficacy
- routine Abx prophylaxis (esp quinolones) may inhibit effectiveness of BCG therapy

What are some of the strategies to improve the toxicity profile of BCG therapy?

- 1) BCG dose reduction
→ Martinez-Pineiro '02 } dose reductions can provide same efficacy
- 2) lengthen instillation interval
→ Bassi '00 } BCG q2weeks for 6 doses shown to be equivalent
- 3) decreased dwell time
→ Andius '00 } 30 min equivalent to 2hrs with better s/e profile
- 4) ABx pre-medication
→ Durek '99 } decreases side effects but also decreases efficacy (esp quinolones)

What factors predict success of BCG therapy?

- 1) **previous response to BCG** } **DON'T** use BCG after 2 induction courses
- 2) **time to failure** } **poor outcomes if recurrence before 1 yr**
- 3) multifocality
- 4) size >5cm
- 5) T1
- 6) age >80 } don't mount response

What are the contraindications to BCG therapy (CHART)?

- **ABSOLUTE (7) }}** "A BIG TIT"
 - **Active** autoimmune disease (eg RA, lupus, etc)
 - **BCG** sepsis in past
 - **Immediately post-TURBT** (risk of intravasation & septic death)
 - **Gross hematuria** (intravasation risk)
 - **Traumatic catheterization** (intravasation risk)
 - **Immunosuppressed & immunocompromised patients** } may now be relative
 - **Total incontinence** (patient will not retain)
- **RELATIVE (6) }}** "TULIPP"
 - **TB** (active or history of)
 - **UTI** (intravasation risk)
 - **Liver disease** (can't get INH if gets septic)
 - **Increased age** (won't mount response)
 - **Poor overall performance status**
 - **Pregnancy & lactation**
- **UNKNOWN RISK**
 - **VUR**
 - pts w/ prosthetics materials
 - anti-TNF meds (?sepsis risk)

What are the side effects of intravesical BCG?

- frequency, dysuria (cystitis) } most common (>75%)
- flu-like symptoms
- UTI
- hematuria
- ureteric obstruction (rare)
- allergic reaction (joint pain, rash)
- BCG sepsis
- solid organ granulomas (epididymitis, prostatitis, hepatitis, pneumonitis, renal GN, osteomyelitis)
- contracted bladder (<1%)

What is the management of BCG toxicity (CHART – Cleveland Clinic approach)?

- grade 1 } moderate symptoms <48hrs → mild/moderate irritative symptoms
 - mild hematuria
 - fever <38.5Rx → possible urine C&S to r/o infection
 - symptom management with **anticholinergics, pyridium, NSAIDs**
- grade 2 } severe symptoms and/or >48hrs → severe irritative symptoms
 - hematuria
 - fever >38.5Rx → same for grade 1 PLUS the following:
 - **urine C&S, CXR, LFTs**
 - ID consult
 - INH 300mg od + rifampin 600mg od **until symptoms resolve**
 - Vitamin B6 (pyridoxine) supplements (50mg OD)
 - dose reduction when instillations resume (1/2 to 1/3 dosing)
- grade 3 } serious complications/sepsis → hemodynamic changes, persistent high-grade fever
 - allergic reactions (joint pain, rash)Rx → same for grade 1 and 2 PLUS the following:
 - INH 300mg od + rifampin 600mg od **for 3-6 months**
 - Vitamin B6 (pyridoxine) supplements (50mg OD)
 - solid organ involvement (epididymitis, liver, lung, kidney, osteomyelitis, prostate)Rx → same for grade 1 and 2 PLUS the following:
 - INH 300mg od + rifampin 600mg od + **ethambutol 15mg/kg od x 3-6mos**
 - Vitamin B6 (pyridoxine) supplementation 50mg OD
 - **consider prednisone 40mg od when response is inadequate**
OR for septic shock (NEVER GIVE ALONE)

What are the different anti-TB meds used for BCG sepsis?

- 1) Isoniazid (INH) } inhibits synthesis of mycolic acids in *M. tuberculosis* by affecting enzyme **mycolase synthetase**
 - 300mg OD } highly active against *M. tuberculosis* and is **bactericidal** at higher []'s
 - } 70% excreted by kidneys but NO RENAL DOSING required
 - } hepatic dosing recommended
 - **hepatotoxicity** in 10-20%
 - } can result in **peripheral neuropathy** d.t. enhanced excretion of Vit B6
 - give **vitamin B6 (pyridoxine)** supplements
 - } can also cause **SLE**
 - 2) Rifampin } Abx isolated from *Streptomyces mediterranei*
 - 600mg OD } inhibits **bacterial RNA synthesis (bactericidal)**
 - } excreted in urine but NO RENAL DOSING required
 - } **hepatotoxicity** is major S/E but can also get **myelosuppression, orange urine**
 - } ++**drug interactions (steroids, BCP), red-man syndrome, pruritus, flu-like symptoms**
 - 3) Ethambutol } inhibits **cell wall synthesis (bacterostatic)**
 - 15mg/kg OD } 80% excreted in urine needs **RENAL DOSING**
 - } can cause **hepatotoxicity, retrobulbar optic neuritis**
 - need routine **visual acuity** checks and **red-green color** checks
- **BCG (*M. Bovis*) resistant to Pyrazinamide so no role**
 - **cycloserine acts fastest BUT causes severe psych symptoms (NOT recommended)**

IFN

How does IFN work in bladder cancer?

- glycoprotein produced in response to antigenic stimuli
- multiple anti-tumour activities
 - 1) **inhibits nucleotide synthesis**
 - 2) **upregulates tumour antigens**
 - 3) **upregulation of anti-angiogenic properties**
 - 4) **stimulation of cytokine release with enhanced T and B cell activation as well as natural killer cell activity**
- IFN- α most widely used

What is the role of IFN as intravesical therapy for bladder cancer?

- as solitary agent it is more expensive and less effective than BCG or intravesical chemo in preventing recurrence of Ta disease, treating CIS, and eradicating residual disease
- **may have additive effects with BCG or allow lower doses of BCG**
- **may have role in combination with BCG for salvage (BCG failures)**
 - 15-20% CR rate
 - 1/3 dosing of BCG

What are the side effects of intravesical IFN?

- frequency, dysuria (cystitis)
- flu-like symptoms
- hematuria
- chronic fatigue
- anemia

What are some other immunotherapeutic agents being studied?

- 1) Keyhole-limpet hemocyanin (KLH) → nonspecific immune stimulant (protein from mollusk)
→ less effective than BCG but better S/E profile
- 2) bropirimine → oral arylpyridinone excreted in urine
→ inducer of host IFN, natural killer cells, and TNF
- 3) mycobacterial cell wall DNA extract → less effective than BCG but better s/e profile & safe to use with disrupted urothelium
- 4) thiosulfinate extracts of garlic → inhibits tumour growth
- 5) mistletoe extract → immuno-stimulatory activity

INTRAVESICAL THERAPY

What are the pros & cons of adjuvant intravesical chemotherapy?

- more popular in Europe than BCG
- PROS } can be used peri-op
 - } no risk of infectious complications → **MAY BE PREFERRED OVER BCG FOR LOW-RISK DISEASE**
 - } decreased recurrence → **CLEAR ADVANTAGE WHEN USED AFTER TURBT**
 - single peri-op dose as effective as 6-8wk maintenance
- CONS } **less effective in PREVENTING PROGRESSION** → 15% vs 37% progression
 - BCG vs doxorubicin (Lamm '91)
- } higher cost than BCG → depends on which agent and in which country

List indications for intravesical chemotherapy.

- post-TURBT
- T1 disease
- high grade disease
- multiple diffuse Ta disease
- large tumour >2cm
- recurrent disease
- maintenance therapy
- unresected disease

What kinds of peri-op intravesical chemotherapy have been studied?

→ NO SIGNIFICANT EFFECT on PROGRESSION

- 1) mitomycin C
 - inhibits DNA synthesis (anti-tumour ABx) } not cell cycle specific
 - usually qweekly for 6-8 weeks at 20-40mg
 - decrease in recurrence of ~38%
 - higher risk of progression cf BCG (7.7% vs 9.4%) → Bohle '04 meta-analysis
 - S/E's } **dermatitis/rash from contact, cystitis, palmar & plantar desquamation, ↓'d bladder capacity, alopecia, diarrhea, contracted bladder (rare), myelosuppression/leukopenia (rare)**
- 2) doxorubicin (adriamycin), epirubicin (derivative of doxo), valrubicin (analog of doxo)
 - ABx that inhibits topoisomerase II + inhibits protein synthesis
 - doxorubicin and epirubicin ~15% better than TUR alone in preventing recurrences
 - valrubicin may have role in BCG refractory CIS where cystectomy is not an option
 - S/E's } **cystitis, GI upset, fever, cardiotoxicity (rare) & contracted bladder (rare)**
- 3) thiotepa
 - alkylating agent not cell cycle specific
 - decreases papillary recurrences by up to 15-40%
 - **small (low molecular weight – 189kD) so has high systemic absorption**
 - S/E's } **myelosuppression (~10-15%), cystitis, fatigue, GI upset, blurred vision, dermatitis from contact, alopecia, infertility**
- 4) novel agents
 - gemcitabine, taxanes

What are some ways to optimize mitomycin C efficacy?

- increase concentration to 40mg in 20cc
- ensure low PVR + pre-dehydration (decrease dilution)
- alkalization of urine
- combined with microwave therapy
- electromotive delivery (given with current) } EMDA

What is the role of combination intravesical chemotherapy?

- studies have NOT shown clear benefit**
- **increased local side effects with only modest outcome improvement**
- no clear advantage for sequential therapy, combo chemotherapy, or combination with BCG
 - except IFN

List the most commonly used intravesical agents for bladder TCC & their respective S/Es.

agent	side effects
BCG	<ul style="list-style-type: none"> - frequency, dysuria (cystitis) - flu-like symptoms - UTI - hematuria - ureteric obstruction (rare) - allergic reaction (joint pain, rash) - BCG sepsis - solid organ granulomas (epididymitis, prostatitis, hepatitis, pneumonitis, renal GN, osteomyelitis) - contracted bladder (<1%)
IFN	<ul style="list-style-type: none"> - frequency, dysuria (cystitis) - flu-like symptoms - UTI - hematuria - chronic fatigue, anemia
MMC	<ul style="list-style-type: none"> - frequency, dysuria, S/P pain (cystitis) - dermatitis/rash from contact - palmar & plantar desquamation - diarrhea - ↓'d bladder capacity or bladder cripple (rare) - myelosuppression/leukopenia (rare) - alopecia
Doxorubicin/adriamycin	<ul style="list-style-type: none"> - frequency, dysuria, S/P pain (cystitis) - UTI - GI upset - fever - cardiotoxicity (rare) - contracted bladder (rare)
thiotepa	<ul style="list-style-type: none"> - frequency, dysuria, S/P pain (cystitis) - myelosuppression (10-15%) - fatigue - GI upset, N/V - dermatitis from contact - blurred vision - infertility - alopecia

MANAGEMENT OF REFRACTORY DISEASE

What are the different ways in which BCG can fail?

- 1) BCG-refractory } non-improving or worsening of disease despite BCG
→ HIGH RISK GROUP
→ should consider CYSTECTOMY if young and healthy
- 2) BCG-resistant } recurrence or persistence of lower degree, stage, or grade after initial induction
BUT resolves after further BCG
- 3) BCG-relapsing } recurrence after initial resolution with BCG

What is the role of routine post-BCG biopsy?

- limited role
- should only be considered in high-risk patients
- if N cysto + N cytology, chance of residual disease limited (Dalbagni et al '99)

What is the significance of a +ve urine cytology at 3months post-BCG?

- could be recurrence of refractory disease
- **BUT, should wait until 6 months to declare BCG failure**
→ response rates rose from 60% to 80% between 3 and 6 months (Herr et al '03)

Which patients are at particular risk of progression despite BCG therapy?

- progression while on therapy
- multiple recurrences
- early recurrence

What is the management of “refractory” non-muscle invasive disease?

- 1) post-intravesical chemo } BCG induction
→ BCG better than 2nd chemo regime
- 2) **post-BCG } 2nd BCG induction**
} still gives 30-50% response
→ if can't tolerate BCG, then salvage chemotherapy
- high risk of failure & progression
→ more than 2 courses of BCG or chemo NOT RECOMMENDED
 - **80% risk of failure and 80% risk of progression**
 - **cystectomy recommended**
 - **if unable to tolerate cystectomy, then IFN + BCG, salvage intravesical valrubicin or gemcitabine, trial protocols**

What is the role of BCG + IFN- α for BCG failures?

- no evidence for primary therapy
- low dose BCG (1/3 dose) + 50-100 million units IFN α } very expensive
- good response rates (~50% at 2yrs)
- better with re-induction and maintenance treatments

What are the arguments in support of “early” cystectomy for non-muscle invasive disease?

- 1) CIS patients that fail BCG have 50% chance of progression
→ however, ~80% of CIS patients do respond to BCG
- 2) early BCG failures (3 months) for T1 tumours have >80% progression rate
→ only 25% progression rate if T1 patient responds at 3months
→ each occurrence of T1 tumour is associated with a 5-10% chance of mets
- 3) 30% of patients are under-staged
- 4) ~90% 10yr survival for those undergoing cystectomy for cT1 disease that actually had pT1 disease
cf those that had progressed on to pT2 disease (64%)

What are the indications for “early” or “timely” radical cystectomy? } } “Let’s DUMP T1G3 ABC”

- LVI
- Diverticulum with high grade TCC } may be amenable to partial cystectomy
- distal Ureteric or prostatic Urethral involvement
- Multifocal CIS
- Patient preference
- **T1G3**
- Access issues } severe urethral strictures, bladder too large, tumour too large
- BCG-refractory superficial disease } CIS, T1 disease, high-grade Ta disease
- Crippled bladder from MMC/BCG
- there may be a future role for p53 and RB tumour markers } STILL UNCLEAR
 - +ve p53 has 75% progression rate (vs 25% for p53 –ve patients)

What is the role of partial cystectomy in refractory non-muscle invasive disease?

- provides more accurate staging → allows lymphadenectomy
- only for those with solitary, non-recurring tumours at dome with no CIS (NB - random Bx’s)

What other options are available for BCG-refractory non-muscle invasive disease?

- 1) photodynamic Rx (PDT) → photosensitizer given 2-3 days before intravesical red laser light (630nm)
 - Rx for 12-20minutes
 - Photofrin at 2mg/kg (iv), HAL (intravesical)
 - 66% response rate for CIS with duration of 37-84 months
 - 50% response rate for Ta with median recurrence of 2-4yrs
 - SIGNIFICANT S/E’s } bladder contracture, irritability, skin sensitivity
- 2) RADs → usually restricted to those refusing cystectomy after intravesical failure or those unsuitable for major surgery
 - **NO BENEFIT FOR CIS**
 - up to 50% will develop progression and high likelihood of death
 - **mainly for palliative therapy**
- 3) microwave chemothermotherapy → microwave therapy with circulating chemotherapy
 - some evidence suggests better than MMC alone
 - may be good for residual disease also
- 4) aggressive TURBT

SURVEILLANCE

What is the recommended surveillance cystoscopy schedule for non-muscle invasive bladder cancer?

- traditional schedule } q3months for 18-24 months
 - } then q6months for the next 2yrs
 - } then annually
 - } reset surveillance schedule with any new tumour
- TaG1 } **absence of recurrence at 3months predicts for very low likelihood of recurrence**
 - } may move to annual evaluation after 1yr from Dx

What is the likelihood of cancer in the setting of persistent +ve cytology but N cysto & imaging?

- **cytology has low sensitivity BUT HIGH SPECIFICITY } pathologist’s interpretation**
- up to 40% found to have malignancy within 2 yrs (Nabi et al 2004)
- bladder washing NOT better than voided specimen or drainage specimen
- false +ve more common if stones or instrumentation
- assess upper tracts } directed cytology +/- ureteroscopy
- think bladder, bladder, bladder (most common – 65%) } need to do random bladder Bx’s
- may also be prostatic urethra } need to do TUR and prostate Bx
- consider 5-ALA cystoscopy

What bladder tumour markers are commercially available?

→ **most have BETTER SENSITIVITY but LOWER SPECIFICITY of urine cytology**

- **high false +ve rate**

→ most markers don't have significant impact on prognosis or disease management

1) NMP22 → detection of nuclear matrix protein 22

→ quantitative & qualitative point-of-care tests are available

2) BTA → detect human complement factor H-related protein

→ quantitative BTA TRAK

→ qualitative point-of-care BTA STAT

3) ImmunoCyt → hybrid of cytology + immunofluorescent assay

→ higher sensitivity than cytology, specificity slightly lower

→ very expensive & interpretation complex/operator-dependent

→ Canadian (Yves Fradet)

4) UroVysion → cytology based test using FISH of DNA probes for chromosomal abN'ties

- looks at chromosomes 3, 7, 17, and 9p21

→ better sensitivity and only marker with equivalent specificity

→ **also detects chromosomal changes before phenotypic expression of tumour } can detect tumours 3-15months ahead**

→ very expensive (\$100)

Table 76-7 -- Commercially Available Markers

Commercially Available Marker	Reagent Cost[*]	Reimbursement	Sensitivity		Specificity	
			Mean (%)	Range (%)	Mean (%)	Range (%)
Cytology	\$2.00	\$25.00	48	16-89	96	81-100
Hematuria dipstick	\$0.60	\$3.00	68	40-93	68	51-97
NMP22	\$25.00	\$35.00	75	32-92	75	51-94
NMP22 BladderChek	\$25.00	\$35.00	55.7		85.7	
BTA stat	\$14.00	\$24.00	68	53-89	74	54-93
BTA TRAK	\$7.00	\$24.00	61	17-78	71	51-89
ImmunoCyt	\$80.00	\$109.00-\$230.00	74	39-100	80	73-84
UroVysion	\$102.47	\$407.00	77	73-81	98	96-100

Data from Andriole et al (2005) and Liou (2006) .

What are some of the investigational markers for bladder cancer?

- Accu-Dx → detects fibrin and its degradation products present in urothelial cancer due to increased VEGF that increases permeability of vessels to proteins

→ higher sensitivity but lower specificity

- telomerase assay → measures telomerase, an protein/RNA complex elevated in malignant cells (increased cell cycle DNA replication)

→ good specificity but low sensitivity

- hyaluronic acid assay → measures HA, a GAG in BM of bladder wall, which is elevated in bladder Ca

→ good sensitivity and decent specificity

- BLCA4 assay

- survivin

- CD44

- mucin 7

- Lewis X

What is the likelihood of upper tract disease after Dx of non-muscle invasive bladder cancer?

- ~2% have upper tract TCC at presentation
- 2-10% develop upper tract TCC during surveillance
- largely depends on grade & stage of tumour } 20-30% in high risk patients
- **appearance of upper tract disease is associated with mortality rates of 40-70%**

What is the role of surveillance imaging for non-muscle invasive bladder cancer?

- INDICATED FOR HIGH-RISK DISEASE (somewhat controversial)
- high grade
- T1
- multifocal
- recurrent disease
- CIS

What is the best imaging study for upper tract surveillance?

- IVP is traditional choice } no info on renal parenchyma & misses small tumours
- retrograde pyelogram } invasive
- CT urography } radiation exposure, contrast exposure, static image
- U/S } misses small tumours and may only find advanced disease (mass or hydronephrosis)

What is the risk of prostatic urethral involvement in patients with non-muscle invasive disease?

- depends on grade and stage
- high risk patients have 10-15% risk within 5yrs & 20-40% risk within 10yrs
- 33% risk in refractory disease

What are the recommended surveillance strategies for non-muscle invasive bladder Ca (CHART)?

- 1) low risk } solitary TaG1
 - cysto q3months for 1yr then annual cysto
 - cytology with each cysto
 - consider stopping cysto after 5 or more yrs
 - no upper tract imaging required
- 2) intermediate risk } multiple TaG1, large tumour, recurrence at 3months
 - cysto q3months for 1-2yrs then q6months or annually after 2yrs
 - cytology with each cysto
 - upper tract imaging for hematuria and for recurrences
- 3) high risk } any high grade, T1, or CIS
 - cysto q3months for 2yrs then q6months for 2yrs then annually for life
 - cytology with each cysto
 - upper tract imaging annually for 2yrs then consider lengthening interval

What are the recommended secondary prevention strategies?

- 1) lifestyle changes
 - smoking cessation } most important
 - increased fluid intake
 - low-fat diet
- 2) chemoprevention
 - high dose multivitamins } promising
 - retinoids and Vit A analogs } higher rates of lung Ca in smokers getting Vit A
 - vitamin B6
 - DFMO
 - COX-2 inhibitors
 - green tea extracts
 - erlotonib (EGF receptor inhibitor)

AUA GUIDELINES 2007 – NON-MUSCLE INVASIVE BLADDER CANCER

What is the difference between clinical staging of bladder Ca and pathologic staging?

- clinical } P/E, imaging, and TURBT pathology
- pathologic } partial or radical cystectomy pathology and LN pathology

What is the difference between guideline standard, recommendation, and option?

→ **Standard** } A guideline statement is a standard if:

- (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions

AND

- (2) there is virtual unanimity about which intervention is preferred

→ **Recommendation** } A guideline statement is a recommendation if:

- (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions

AND

- (2) an appreciable but not unanimous majority agrees on which intervention is preferred

→ **Option** } A guideline statement is an option if:

- (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions

OR

- (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made

What are the guideline statements on an index patient with an abN growth but NO DIAGNOSIS?

→ **standards**

- **Bx is essential**
- **complete eradication of all visible tumours**
- **if bladder Ca Dx is made, surveillance cysto should be performed**

→ **options**

- single dose of intravesical chemo post-TURBT

What are the guideline statements on a patient with a SMALL, LOW-GRADE Ta tumour?

→ **recommendations**

- **single dose of intravesical chemo post-TURBT**

What are the guideline statements on a patient with MULTIFOCAL and/or LARGE VOLUME, LOW-GRADE Ta tumour or a patient with RECURRENT LOW-GRADE Ta tumour?

→ **recommendations**

- **induction BCG or MMC to prevent or delay recurrence**

→ **options**

- maintenance BCG or MMC (no difference b/w the two for this group)

What are the guideline statements on a patient with HIGH-GRADE, Ta, T1, and/or CIS tumours?

→ **standards**

- **re-TURBT for T1G3 before intravesical Rx (~40% risk of muscle-invasive dz)**

→ **recommendations**

- **induction BCG + maintenance (BCG superior to MMC for this group)**

→ options

- immediate cystectomy can be considered in some patients

What are the guideline statements on a patient with RECURRENT HIGH-GRADE, Ta, T1, and/or CIS tumours AFTER intravesical therapy?

→ **standards**

- **re-TURBT for T1G3 before intravesical Rx (~40% risk of muscle-invasive dz)**

→ **recommendations**

- **cystectomy should be considered**

→ options

- further intravesical therapy is an option

Chapter #77 – Management of Invasive and Metastatic Bladder Cancer

PRESENTATION, DIAGNOSIS, AND EVALUATION

What are the common signs & symptoms of invasive and metastatic bladder cancer?

→ often same signs and symptoms as superficial bladder cancer

- hematuria → micro or gross

→ up to 80% of patients

- irritative voiding symptoms

- constitutional symptoms

→ **80% of pts with muscle-invasive disease present de novo } only ~20% are progressions**

What is the work-up of suspected invasive TCC of the bladder?

- 1) Hx & P/E } RFs (“COBRA SCARS”), signs/symptoms of mets, etc

- 2) lab tests } CBC, lytes, creatinine, LFTs, Ca profile, ALP, urine cytology

- 3) imaging } CXR + CT +/- bone scan +/- CT chest

- 4) surgical staging } TURBT + EUA

} consider 2nd TURBT

What is the role of TURBT?

- required to diagnose muscle invasive bladder cancer

- if invasive bladder cancer is suspected, axial staging should be done prior to TURBT because post-op imaging may be affected by surgery

What is the role of bimanual exam?

- sensitive and inexpensive

- performed **before & after tumour resection**

- presence of palpable mass after TURBT correlates w/ stage T3 & prognosis after Rx
→ stage T4 if fixed

What is the role of re-TURBT?

- 1) recommended by some to assess degree of tumour burden after initial Dx

→ especially with T1G3 on initial Dx

→ risk of \geq T2 disease on re-TURBT is 40-60% if no muscle in 1st resection

→ risk of \geq T2 disease on re-TURBT is 20-30% if +ve muscle in 1st resection

- 2) provides info about residual disease

→ reduction of staging to p0 on 2nd TURBT assoc'd with favorable long-term survival

- 3) recommended for pts with \geq T2 disease who are candidates for alternatives to standard cystectomy

AXIAL IMAGING

What imaging modalities are used to stage invasive bladder cancer?

- 1) CT → **tends to understage advanced disease**
 - doesn't alter surgical management in most cases
 - can't accurately identify microscopic extravesical disease
 - correlates with pathologic Dx on cystectomy in 65-80% of cases
 - detects metastatic disease in regional LNs in 50-85%
- 2) MRI → ideal for renal insufficiency patients } risk of NSF
 - **similar inability to detect microscopic extravesical disease as CT**
 - **understaging & overstaging similar to CT → 30%**
- 3) Bone scan → not necessary for clinically organ-confined, muscle-invasive disease
 - **recommended only in pts with signs/symptoms suggestive of bone mets**
- 4) PET scan → based on uptake of fluorodeoxyglucose by tumour cells
 - better at detecting LN mets than staging primary lesions (tracer in urine obscures detail of bladder wall)
- 5) Laparoscopic staging → some recommend lap pelvic lymphadenectomy as staging technique
 - criticized for incidences of port site recurrence
 - may be better to do single-stage open lymphadenectomy w/ radical cystectomy

*** **presence of hydro is treated as T2 disease** ***

*** **pathologic stage of disease correlates strongly with patient's outcome after interventions** ***

RADICAL CYSTECTOMY FOR INVASIVE BLADDER CANCER

What are the standard management options for invasive bladder cancer?

- 1) radical cystectomy +/- neoadjuvant chemo +/- adjuvant chemo
- 2) RADs + chemo
- 3) bladder sparing protocols } eg aggressive TURBT + CHEMO + RADs, radical TURBT + surveillance, aggressive TURBT +/- partial cystectomy, interstitial RADs, etc

What are the indications for radical cystectomy (coupled with en bloc pelvic lymphadenectomy)?

- cystoprostatectomy for men
- anterior exenteration for women
- "PIPE"
 - Prostatic stromal involvement
 - Invasive disease ($\geq T2$) without mets
 - Palliation for metastatic bladder Ca w/ significant local symptoms (eg refractory hemorrhage)
 - Early Cystectomy ("Let's DUMP T1G3 ABC") } LVI, diverticulum, ureteral or urethral, multifocal CIS, patient preference, T1G3, access issues, BCG refractory, crippled

What are the important principles of radical cystectomy?

- 1) always includes bilateral pelvic lymphadenectomy
- 2)a) in men, includes en bloc removal of bladder & prostate
 - b) in women, anterior exenteration involves removal of uterus, fallopian tubes, ovaries, urethra, and a segment of anterior vaginal wall
- 3) nerve-sparing cystoprostatectomy can be done to preserve erectile function w/o compromise of oncologic principles
 - ligate prostatic pedicles so as to preserve soft tissue and NVB adjacent to tips of SVs

How common is urethral recurrence AFTER RADICAL CYSTECTOMY?

→ **more common after diversion than orthotopic neobladder (likely biased groups)**

- **in men** → **7-10% urethral recurrence rate (usually within first 24 months)**

→ 5yr probability of urethral recurrence is 5% if no prostate involvement

→ ~15% 5yr recurrence rate if prostatic urethral or ductal involvement

→ highest rate of anterior urethral recurrence with prostatic stromal invasion (20-60%)

- **in women** → **2-12% have urethral involvement at time of cystectomy**

→ **1-2% recurrence rate**

→ presence of cancer at BN correlates with presence of urethral cancer

What are the indications for urethrectomy?

→ in men } 1) ?CIS or gross tumour involving urethra (esp. prostatic urethra or stroma)

2) +ve distal urethral margin

3) urethral recurrence post-cystectomy

→ in women } 1) ?CIS or gross tumour involving BN, urethra, or anterior vaginal wall

2) +ve distal urethral margin

3) urethral recurrence post-cystectomy

→ required in <5% of patients

→ CIS & multifocality NOT risk factors for urethral involvement

→ RFs for urethral recurrence include:

- prostatic stromal involvement in men

- BN or anterior vaginal wall involvement in women

- cutaneous diversion

List contraindications for continent orthotopic neobladder } “RUM RAIDS Liver”

→ **ABSOLUTE** } } } “RUM”

- **Renal impairment (irreversible)** } serum creatinine >2mg/dL (>180 µmol/L),
creat clearance <60mL/min or proteinuria, inability
to acidify urine, inability to concentrate urine

- **Urethral TCC** prior to cystectomy

- **Margin +ve** (intra-op distal urethral)

→ **RELATIVE** } } } “RAIDS Liver”

- **RADs** (extensive)

- **Age** or limited life expectancy (T3 or N+ disease should not be excluded automatically)

- **IBD**

- **Dexterity** issues (inability to do CIC, if necessary eg mental or physical impairments)

- **Short bowel**

- **Liver failure**

What is the role of ureteral margin frozen-sections?

- standard at time of radical cystectomy, prior to urinary tract reconstruction

- **resect +ve margins, leave CIS } recurrence at anastomosis is rare, even if +ve for CIS**

→ debatable whether clearing ureteral margins at the time of cystectomy provides any long-term survival benefit

→ if papillary disease found at margin, perform ureteroscopy

What is the 10yr disease-specific survival data on patients post-cystectomy?

- **pT2** → ~65-75%

- **pT3** → ~30-50%

- **pT4** → ~20-30%

What is the role of pelvic lymphadenectomy in radical cystectomy?

- beneficial for 2 main reasons:
 - 1) staging → info on local extent of disease
 - 2) curative → high rates of long-term survival in patients with limited nodal burden
- **risk of pelvic LN mets increases with tumour stage**
 - pT2 → 10-30%
 - pT3 or higher → 30-65%
- **obturator (75%) & external iliac (65%) LNs are most commonly involved**
 - common iliac and presacral nodes are less commonly involved
- **among those with +ve LN mets, the number of LNs removed is prognostic** (Stein et al '03)
 - 10yr recurrence-free survival = 25% if ≤15 LNs removed; 36% if >15 LNs removed
 - 10 yr recurrence-free survival = 10% if ≤8 LNs removed; 40% if >8 LNs removed
- **+ve LN density has also been shown to be prognostic (+ve LNs / total LNs removed)**
 - 10yr recurrence-free survival = 17% if >20%; 43% if ≤20% (Herr 2003, Stein et al 2003)
- **extranodal extension is a very bad prognostic finding**
- sending LNs as separate packets, increases likelihood of finding +ve LNs } ?survival impact

What is the role of extended LN dissection?

- involves dissection of distal para-aortic & para-caval LNs (up to IMA), as well as **pre-sacral and common iliacs (JCO - Skinner)**
- standard pelvic LN dissection is external iliac & obturator LNs up to common iliacs
 - 1) same percentage of patients with node +ve disease cf standard pelvic lymphadenectomy
 - 2) greater total number of LNs } may be better prognosis

What is the follow-up after radical cystectomy?

- surveillance required for:
 - 1) tumour recurrence
 - 2) complications related to the use of bowel as urinary tract
- timing is controversial but involves P/E, CBC, lytes, creatinine, CXR, U/S or CT abdo/pelvis
 - annual for pT1
 - q6/12 for pT2
 - q3/12 for pT3
- periodic urethral cytology and, when indicated, biopsy for retained urethra

What are the potential complications of radical cystectomy?

- **mortality } 1-3%** → **overall complication rate } up to 25-35%**
- intra-op
 - major bleeding/hemorrhage (<1%)
 - rectal injury (1%)
 - bowel injury
 - obturator nerve injury
- early post-op
 - atelectasis
 - delayed bleed
 - urine leak
 - DVT
 - pneumonia
 - PE (2%)
 - wound infection
 - bowel anast leak
 - ileus/bowel obstruction
 - MI
- delayed post-op
 - bowel obstruction (4-10%)
 - ED
 - incontinence (more M)
 - obstruction (more F)
 - conduit stones
 - renal stones
 - fistula
 - wound dehiscence/hernia
 - anast strictures (3%)
 - UTIs/pyelo
 - metabolic disorders
 - vitamin deficiencies (B12 from terminal ileum)
 - stomal issues

What is the management of a rectal injury during radical cystectomy?

- colostomy if } gross spillage
- } previous RADs
- } inadequate bowel prep
- primary repair +/- colostomy +/- gen sx consult
 - mucosa then muscle & serosa with 3-0 vicryl } place omentum/fat over repair
 - irrigate pelvis with NS or bacitracin
 - JP drain + post-op Abx } consider anal dilation

*** Gen Sx repairs rectum in 1 layer only ***

*** should form of urinary reconstruction make a difference? ie conduit vs neobladder (risk of fistula) ***

What are the RFs for wound dehiscence?

- infection
- poor nutrition
- DM
- steroid use
- pulmonary disease
- RADs
- surgical technique

List indications for radical cystectomy for non-muscle invasive disease } “Let’s DUMP T1G3 ABC”

- **LVI**
- **D**iverticulum with high grade TCC } may be amenable to partial cystectomy
- distal **U**reteric or prostatic **U**rethral involvement
- **M**ultifocal CIS
- **P**atient preference
- **T1G3**
- **A**ccess issues } severe urethral strictures, bladder too large, tumour too large
- **BCG**-refractory superficial disease } CIS, T1 disease, high-grade Ta disease
- **C**rippled bladder from MMC/BCG

What are the different options for urinary diversion after radical cystectomy?

- incontinent
 - conduit } eg ileal, colon, jejunal
- continent
 - neobladders } eg Studer ileal neobladder, Le Bag ileocolic pouch, Mainz pouch, Ghoneim, T pouch ileal neobladder, Kock ileal neobladder, Camey II
 - cutaneous reservoirs } eg Indiana pouch, Kock pouch, Mainz I, Double T pouch
 - rectal diversions } eg ureterosigmoidostomy, Mainz II, folded rectosigmoid, rectal bladder

ADJUNCTS TO STANDARD SURGICAL THERAPY

What is the role of **NEOADJUVANT RADs**?

- thought is to treat local micromets, downstage unresectable tumours, & improve local control
- randomized data shows that for T3 disease, though local control may be improved, there is
NO CLEAR SURVIVAL ADVANTAGE

What is the role of NEOADJUVANT CHEMO?

- potential advantages include:
 - 1) allows a demonstration of tumour chemosensitivity
 - 2) may downstage otherwise inoperable lesion
 - 3) may treat micromets while patient isn't debilitated post-cystectomy
 - disadvantages include:
 - 1) delay in definitive local therapy
 - 2) error resulting from a primary reliance on clinical staging (10% overstaging)
 - **randomized trials DEMONSTRATING SIGNIFICANT BENEFIT of neoadjuvant chemotherapy**
 - NEJM '03 (Grossman-SWOG)
 - randomized to cystectomy VS cystectomy + **NEOADJUVANT MVAC** (3cycles)
 - 317 patients with T2 to T4a patients (NoMo)
 - **31 months median survival benefit (46 vs 77 months)**
 - significantly more patients had no residual disease (pTo) (38% vs 15%)
 - JCO '05 (von der Maase)
 - 405 patients with locally advanced (T4b, N2-3) or metastatic (M1) disease
 - randomized to **ADJUVANT MVAC** vs GC } after cystectomy, RADs, or BCG
 - **similar overall survival & progression-free survival but less toxicity w/ GC**
- *** THERE IS NO STUDY SHOWING NEOADJUVANT GC IMPROVES SURVIVAL ***

What is the role of ADJUVANT CHEMO?

- for patients with pathologically staged tumours with evidence of mets
- potential advantages include:
 - 1) reduce likelihood of local recurrence
 - 2) reduce distant metastatic relapse
- disadvantages include:
 - 1) delay in systemic therapy in patients with proven mets
 - 2) hard to assess tumour response to Rx in absence of residual disease on imaging
 - 3) post-op complications interfering with completion of adjuvant protocol
 - 4) reduced willingness of patient to participate in adjuvant chemo post-op
- cisplatin-based adjuvant chemo may provide a survival advantage in T3 disease
- 4 randomized trials } Skinner et al '91, Stockle et al '95, Studer et al '94, Freiha & Torti '96
- **NO DEFINITIVE DATA } consider for advanced disease (pT4 and N+ pT3)**
 - } may have ~10% survival benefit at 3yrs

What is the role of **PERI-OP CHEMO**?

- **NO DIFFERENCE** between peri-op chemo (2 cycles MVAC pre and 3cycles MVAC post) and post-op chemo (5cycles MVAC)
 - Logothetis et al '96 – MD Anderson

ALTERNATIVES TO STANDARD THERAPY

What are some of the alternatives to standard therapy for invasive bladder cancer?

- 1) RADs (55-65 Gy)
 - no head-to-head randomized trials
 - controls locally invasive disease in 30-50% → HYPER-fractionation may be better
 - **LESS EFFECTIVE if anemic**
 - **not good option for T3b, T4, and if presence of hydronephrosis**
- 2) Bladder Preservation Protocols
 - aggressive TURBT + CHEMO + RADs
 - only complete responders are advanced to full-dose regimes
 - allows for salvage cystectomy for incomplete responders before they get full-dose RADs
 - 40-50% 5yr overall survival
 - TURBT + CHEMO
 - 75% 5yr disease-specific survival after TURBT + chemo if first cysto negative
 - TURBT + Partial Cystectomy +/- CHEMO
 - for select small, low-stage T2 lesions
 - 'radical' TURBT with -ve tumour bed and normal peripheral Bx's has survival rates similar to radical cystectomy (Solsona et al '98)
 - Herr JCO '01
 - 432 pts with T2 got re-TURBT
 - 281 had residual T2 and got cystectomy
 - 151 had T0-T1 } 52 had cystectomy while 99 were observed
 - 10yr disease-free survival = 76% for observed vs 71% for immediate cystect
- 3) Interstitial RADs
 - pre-op RADs/partial cystectomy/TURBT + placement of iridium 192 wires
 - overall survival rates for T1-T2 is 60-80%
 - complications include delayed wound healing, fistula formation, hematuria, & chronic cystitis
- 4) Intra-arterial Chemo
 - increased dose delivery with reduced toxicity } no large studies
- 5) Hyperthermia + CHEMO
 - hyperthermia to improve anti-neoplastic activity of chemo or rads
 - NO BENEFIT shown by Dutch group in 2000

What is the role of TURBT for muscle-invasive disease?

- **INADEQUATE for definitive treatment of muscle-invasive disease**
- NO randomized studies to compare TUR alone with cystectomy
- may be an option for those refusing or unsuitable for cystectomy; +/- adjuvant Rx (eg chemo, rads, etc)
- **~10% of patients are pT0 at time of cystectomy (Herr '92)**
- up to 80% 5yr survival for TURBT alone in select patients (Solsona et al '92)

What are the motivations FOR bladder preservation protocols for muscle-invasive bladder cancer?

- 1) micromets won't be treated with local therapy without concomitant systemic therapy
- 2) removal of bladder in asymptomatic patient with mets isn't necessary, doesn't improve QOL, and delays delivery of systemic therapy

What are the arguments AGAINST using bladder preservation protocols?

- 1) preservation protocols rely on clinical and not pathological staging → prone to error
- 2) local recurrence and complications from local relapse or failure cause significant M&M
- 3) orthotopic bladder reconstruction now widely available and provides excellent QOL

What are the contraindications against bladder sparing protocols?

- 1) presence of hydro
- 2) CIS → responds poorly to multimodal therapy
- 3) tumour that can't be completely resected by TURBT

What are the general criteria for selective bladder sparing protocols

- 1) muscle invasive disease
- 2) absence of hydro
- 3) N renal function
- 4) N CBC
- 5) suitable candidate for cystectomy
- 6) absence of mets on imaging

MANAGEMENT OF METASTATIC BLADDER CANCER

What is the role of CHEMO in the management of metastatic bladder cancer?

- **CHEMO is routine treatment for metastatic bladder cancer**
- **asymptomatic with N+ disease**
 - **best response (20% complete response rate)**
 - **if symptomatic and/or visceral mets, poor response to chemo**
- MVAC most common regime (MTX, vinblastine, doxorubicin/adriamycin, cisplatin)
 - 20% complete response
 - long-term disease-free survival rare } 3% at 6yrs (Saxman JCO '97)
 - assoc'd w/ significant toxicity } **20% neutropenic fever**
 - 3-4% death from sepsis
 - } mucositis, cardiotoxicity (adriamycin), neurotoxicity, etc
 - } **dose-limiting toxicity is BM suppression & mucositis**
 - can dose escalate with GM-CSF (Neupogen)
 - decompress neobladder/conduit } ↑'d absorption of MTX

What newer chemo regimes exist for metastatic bladder cancer?

- gemcitabine monotherapy → 25% complete response
- **gemcitabine + cisplatin** → **similar survival outcomes with less toxicity cf MVAC**
 - **BUT shown only in ADJUVANT setting (cf MVAC)**
 - most significant S/E's are thrombocytopenia & neutropenia (in almost 50%) and mucositis
 - 40% partial or complete response
- taxanes in combination therapy → anti-microtubule agent
 - 25-83% response rates
- gallium nitrate → naturally occurring metal
 - 10-50% response rates in Phase II trials but ++++ toxicity
- trimetrexate → antifolate
 - may be useful in patients resistant to MTX

List 3 of the most common CHEMO regimes used for bladder cancer.

- MVAC } limited by BM suppression, cardiotoxicity, mucositis
- GC } limited by BM suppression, nephrotoxicity, mucositis
- CMV } limited by BM suppression, nephrotoxicity

LOCAL SALVAGE AND PALLIATIVE THERAPY

What is the role of salvage cystectomy?

- after conservative or primarily non-surgical forms of therapy have produced partial response with residual disease confined to bladder
 - ~20% survival
- **NOT indicated if residual extra-vesical disease**

ALKYLATING AGENTS

Eg cisplatin, carboplatin, cyclophosphamide, ifosfamide, thiotepa, estramustine, nitrogen mustard

Mode of action: directly damages DNA

Toxicities:

Cisplatin → nephrotoxicity, ototoxicity, **peripheral neuropathy**, mild cytopenia, N/V, Raynaud's, gonadal dysfxn

Carboplatin → ototoxicity, nephrotoxicity, hepatitis, hypoMg, hypoK, peripheral neuropathy, **myelosuppression** (worse than cisplatin)

Cyclophosphamide → cytopenia, **hemorrhagic cystitis**, cardiomyopathy, spermatogenic arrest, SIADH

ANTI-METABOLITES } } } "GM-5"

Eg MTX, gemcitabine, 5-FU

Mode of action: interfere with DNA and RNA division

Toxicities:

MTX → myelosuppression, nephrotoxicity, pulmonary fibrosis (minimized by leukovorin), stomatitis

Gemcitabine → nephrotoxic, hepatotoxic, cytopenia, alopecia

ANTI-TUMOUR ANTIBIOTICS } } } "-mycin's"

Eg bleomycin, doxorubicin/adriamycin, mitoxantrone, mitomycin C, actinomycin-D

Source: from byproducts of fungus Streptomyces

Mode of action: interfere with enzymes involved in DNA replication, preventing RNA synthesis

Toxicities:

Bleomycin → **pulmonary fibrosis**, pneumonitis fevers and chills (**NO MYELOSUPPRESSION**)

Doxorubicin/adriamycin → cytopenia, **cardiotoxicity**

Mitoxantrone → **cardiotoxicity**, cytopenia, mucositis

MITOTIC INHIBITORS/PLANT ALKALOIDS } } } "VET"

Eg vinca alkaloids (vinblastine, vincristine), taxanes (docetaxel), etoposide

Source: plant derivatives

Mode of action: antimicrotubule agents

Toxicities:

Docetaxel → cytopenia, redness/soreness of **palms and soles**, peripheral neuropathy, fluid retention

Vinblastine → neurotoxicity, BM suppression, glossitis

Vincristine → neurotoxicity, alopecia (**NO MYELOSUPPRESSION**)

Etoposide → mucositis, hepatitis, pneumonia, BM suppression, **secondary malignancies**

Chapter #78 – Surgery for Bladder Cancer

TURBT

What are the goals of TURBT?

- 1) diagnostic
 - obtain tissue for histologic examination to determine type and extent of disease
- 2) therapeutic
 - definitive treatment of all macroscopic non-invasive disease
 - management of superficially invasive (T1) disease
 - treatment of muscle invasive disease in patients unsuitable for radical cystectomy

What is involved in the pre-op evaluation prior to TURBT?

- 1) Hx and physical
 - HPI
 - PMHx
 - RFs (COBRA SCARS) } cyclophosphamide, occupational exposures, RADs, Smoking, chronic UTIs, analgesic abuse, renal Tx, Schisto, etc
 - signs or symptoms of metastatic disease
- 2) P/E
 - bimanual exam pre and post-TURBT essential
- 3) lab tests
 - blood work } CBC, lytes, creatinine, LFTs, Ca profile, ALP, coag's
 - urine cytology
 - urine C&S } ensure sterile C&S prior to TURBT
- 4) imaging
 - upper tract imaging
 - consider staging CT before if suspicious of invasive disease (artifact post-TURBT)

What methods are used to avoid the obturator nerve reflex?

- GA + muscle relaxant
- bipolar cautery loop to minimize conduction
- spinal anesthesia (obturator block) to minimize adductor muscle spasm
- laser fulguration
- avoid overfilling of bladder

What are the best electrical current settings?

- cutting } undamped current from **tube oscillator circuit**
- coag } highly damped spark-gap current from **spark-gap oscillator circuit**
- blended improves hemostasis

What is the role of TURBT for muscle-invasive disease?

- **INADEQUATE for definitive treatment of muscle-invasive disease**
- NO randomized studies to compare TUR alone with cystectomy
- may be an option for those refusing or unsuitable for cystectomy; +/- adjuvant Rx (eg chemo, rads, etc)
- **~10% of patients are pT0 at time of cystectomy (Herr '92)**
- up to 80% 5yr survival for TURBT alone in select patients (Solsona et al '92)

Which patients may be eligible for TURBT alone for muscle-invasive disease?

- all lesions must be completely resectable transurethrally
- essential to re-resect to assess for residual cancer
- 1) unsuitable for radical cystectomy
- 2) small, solitary, papillary low grade T2
- 3) minimal stage T3a lesions <2cm
- 4) no muscle-invasive disease in tumour base tissue

What is the role of post-TURBT intravesical chemotherapy?

- eg mitomycin C 40mg in 40cc NS for 1hr
- **decreases recurrences by >50%**
- **no effect on progression**
- cannot give BCG post-TURBT

What are the potential complications of TURBT?

- | | | | | | |
|-------------|---|--------------------------------|------------|---|---------------------------------------|
| 1) intra-op | } | severe bleeding (<5%) | 2) post-op | } | delayed bleeding +/- clot retention |
| | } | perforation (<5%) | | } | seeding from perforation (very low) |
| | } | obturator reflex | | } | irritative voiding symptoms |
| | } | urethral false passages/trauma | | } | infection |
| | } | TUR syndrome | | } | urethral strictures |
| | } | sepsis | | } | ureteral orifice scarring/obstruction |
| | | | | } | foot drop (common peroneal nerve) |

What is the management of bladder perforations?

- small perforations } no clinical significance
- } catheter drainage + Abx as needed
- large extraperitoneal perforations } catheter drainage + Abx
- } may require percutaneous drain
- intraperitoneal perforations } may get away with catheter drainage + Abx + close monitoring
- } if risk of bowel injury, loss of tumour chip or ongoing signs
- of peritoneal irritation despite catheter, LAPAROTOMY
- } percutaneous peritoneal drainage and lap repair are options

SURGICAL APPROACHES

What are the surgical approaches to the bladder?

- 1) transverse → Pfannenstiel or Cherney
- 2) vertical

What is the blood supply to the bladder

- | | |
|---|--|
| → from anterior branch of internal iliac artery | |
| - superior vesical branch | \ |
| - inferior vesical branch | } |
| - branches from inferior gluteal and obturator | / |
| | can tolerate extensive mobilization due to blood supply eg psoas hitch |

RADICAL CYSTECTOMY IN THE MALE

What are the indications for radical cystectomy in males? } } } “PIPE”

- goal if for surgical cure, unless for palliation
- **P**rostatic stromal involvement
- **I**nvasive disease ($\geq T2$) without mets
- **P**alliation for metastatic bladder Ca w/ significant local symptoms (eg refractory hemorrhage)
- **E**arly Cystectomy (“Let’s DUMP T1G3 ABC”) } LVI, diverticulum, ureteral or urethral, multifocal CIS, patient preference, T1G3, access issues, BCG refractory, crippled

What is the pre-op evaluation prior to radical cystectomy for men?

- 1) Hx and physical
 - r/o significant co-morbidities that would prevent surgery
 - r/o mets
 - stop smoking and stop ASA
- 2) lab tests
 - CBC, lytes, creat, coag’s, LFTs, Ca profile, ALP
- 3) imaging
 - CXR } chest CT if symptoms or abnormal CXR
 - CT abdo/pelvis
 - bone scan } if symptomatic or elevated ALP
 - GI studies eg barium enema, colonoscopy } if hx of GI disease that may affect type of urinary diversion
- 4) TUR
 - TURBT + bimanual EUA
 - multiple bladder Bx’s } debatable
 - prostatic urethral Bx (to r/o need for urethrectomy) } NOT RECOMMENDED
- 5) stoma therapy consult
- 6) peri-op
 - anticoagulation
 - bowel prep (eg Mg citrate or PicoSalax) +/- Abx (debatable)

Describe the main extirpative steps of a radical cystectomy in a male.

- explore peritoneal cavity for mets
- identify, ligate, divide urachus (median umbilical ligament) below umbilicus
- identify, ligate, divide vas bilaterally
- bilateral pelvic lymphadenectomy } STANDARD vs EXTENDED LND
 - may involve ligation of branches of internal iliac that feed bladder eg superior vesical
- identify and mobilize ureters } lateral blood supply to pelvic ureter; medial for abdo ureter
 - } divide close to bladder
- send distal ureteric margins for frozen section } re-resect if evidence of TCC, CIS debatable
- incise posterior peritoneum and develop plane between bladder and rectum } Denonvillier’s
- dissect lateral pedicles of bladder } divide superior and inferior vesical vessels
- if candidate for nerve-preservation then retrograde dissection of prostate can be done
 - TCC usually doesn’t extend beyond prostate so can often preserve nerves
- if urethrectomy indicated, dissect urethra under symphysis to facilitate perineal dissection
 - tie off urethra at level of prostatic apex to avoid spillage of urine
- if continent diversion planned, send frozen-section of prostatic urethra and distal margin
 - no continent diversion if margins +ve for TCC

What are the borders of the pelvic lymphadenectomy performed during a radical cystectomy?

- lateral → genitofemoral nerve
- superior → bifurcation of common iliac artery
- inferior → endopelvic fascia and node of Cloquet
- medial → bladder
- posterior → internal iliacs
- *** extended lymphadenectomy includes nodes along common iliacs up to aortic bifurcation ***
- *** some argue up to IMA + presacral nodes ***

What are the potential benefits of extended lymphadenectomy during radical cystectomy?

- improves survival in patients with LN -ve disease and limited LN mets (Herr et al '02)
- separate packets are better than en bloc resection of nodal package

What are the potential complications of radical cystectomy?

→ overall complication rate } up to 25-35%

→ mortality } 1-3%

→ intra-op

- major bleeding/hemorrhage (<1%)
- rectal injury (1%)
- bowel injury
- obturator nerve injury

→ early post-op

- atelectasis
- PE (2%)
- DVT
- pneumonia
- delayed bleed
- wound infection
- urine leak
- bowel anast leak
- ileus, SBO
- MI

→ delayed post-op

- bowel obstruction (4-10%)
- wound dehiscence/hernia
- fistula
- anast strictures (3%)
- conduit stones
- renal stones
- UTIs/pyelo
- ED
- incontinence (more M)
- obstruction (more F)
- metabolic disorders
- stomal issues

List the indications for “early” or “timely” radical cystectomy }}} “Let’s DUMP T1G3 ABC”

- LVI
- Diverticulum with high grade TCC } may be amenable to partial cystectomy
- distal Ureteric or prostatic Urethral involvement
- Multifocal CIS
- Patient preference
- T1G3
- Access issues } severe urethral strictures, bladder too large, tumour too large
- BCG-refractory superficial disease } CIS, T1 disease, high-grade Ta disease
- Crippled bladder from MMC/BCG

- wound infection
- corpora cavernosal injuries
- bleeding/hematoma
- injuries to internal pudendal arteries during dissection of cephalad portion of urethra

RADICAL CYSTECTOMY IN THE FEMALE

What are the indications for radical cystectomy in females? } } } “PIE”

- goal if for surgical cure, unless for palliation
- Palliation for metastatic bladder Ca w/ significant local symptoms (eg refractory hemorrhage)
- Invasive disease ($\geq T2$) without mets
- Early Cystectomy (“Let’s DUMP T1G3 ABC”) } LVI, diverticulum, ureteral or urethral, multifocal CIS, patient preference, T1G3, access issues, BCG refractory, crippled

What are the advantages of the anterior approach in women, as opposed to a vaginal approach?

- allows simultaneous pelvic LN dissection
- allows simultaneous urethrectomy
- allows dissection of uterus, ovaries, fallopian tubes
- allows partial vaginectomy

What is the pre-op evaluation prior to radical cystectomy for women?

- 1) hx and physical
 - r/o significant co-morbidities that would prevent surgery
 - r/o mets
 - stop smoking and stop ASA
- 2) lab tests
 - CBC, lytes, creat, coag’s, LFTs, Ca profile, ALP
- 3) imaging
 - CXR } chest CT if symptoms or abnormal CXR
 - CT abdo/pelvis
 - bone scan } if symptomatic or elevated ALP
 - GI studies eg barium enema, C-scope } if hx of GI disease that may affect type of diversion
- 4) TUR
 - TURBT + bimanual EUA
 - multiple bladder Bx’s } debatable
- 5) stoma therapy consult
- 6) peri-op
 - anticoagulation
 - bowel prep (eg Mg citrate or PicoSalax) +/- Abx (debatable)

How common is urethral involvement in females with bladder cancer?

- **~2-5% of bladder cancers in women have urethral involvement**
- bladder neck involvement is most significant RF } 40% w/ BN involvement had urethral involvement

What are the RFs for bladder cancer involving the urethra, vagina, and/or cervix?

- extremely large tumours
- tumours involving bladder neck
- diffuse CIS
- locally advanced tumours

What is the role for urethra-sparing, vaginal-sparing radical cystectomy in women?

- indicated in certain patients }
 - a) continent neobladder planned
 - b) young, sexually active patient with small tumour
 - c) small tumour near dome
- pubourethral ligaments NOT divided } maintains post-op continence
- only initial 1cm of urethra removed
- avoidance of extensive dissection preserves muscularity & innervation of urethral sphincter
- lateral pedicles of bladder are divided anterior/ventral to vesicovaginal jxn to preserve NVB to clitoris
- vesicovaginal plane developed in retrograde fashion along anterior vagina to vesicocervical jxn

Describe the main extirpative steps of a radical cystectomy in a female.

- explore peritoneal cavity for mets
- identify, ligate, divide urachus (median umbilical ligament) below umbilicus
- identify, ligate, divide round ligament bilaterally
- identify, ligate, divide ovarian vessels in infundibulopelvic ligament
- bilateral pelvic lymphadenectomy } boundaries are debated (role of extended LN dissection)
→ may involve ligation of branches of internal iliac that feed bladder eg superior vesical
- identify and mobilize ureters } lateral blood supply to pelvic ureter; medial for abdo ureter
} divide close to bladder
- send distal ureteric margins for frozen section } re-resect if evidence of TCC
} CIS is debatable
- incise posterior peritoneum and develop plane between uterus and rectosigmoid } cul-de-sac
- mobilize vagina off rectosigmoid colon } sponge stick in vagina assists dissection
- identify cervix in posterior vagina, incise vagina below cervix } may need to ligate, divide
cardinal ligaments
- if tumour small, avoid resection of large segments of vagina } preserves adjacent pelvic plexus w/
autonomic nerves
} pudendal nerve supplies
rhabdosphincter
- dissect suspensory ligaments of urethra and incise endopelvic fascia
- ligate and divide dorsal vein of clitoris then mobilize urethra
- if urethrectomy is planned, divide pubourethral suspensory ligaments (like puboprostatics)
- if neobladder planned, pubourethral ligaments are preserved and only BN and proximal 1cm
of urethra are removed
- if tumour is small, can spare vagina } reconstruct w/ skin graft, muscle flap, bowel (colon)
- divide urethra and small portion of vagina to complete anterior exenteration
→ ovaries, tubes taken en bloc
- JP drain
- vaginal packing for max 48hrs

What are the potential complications of radical cystectomy in a female?

- overall complication rate } up to 25-35%
- mortality } 1-3%
- intra-op
 - major bleeding/hemorrhage (<1%)
 - rectal injury (1%)
 - bowel injury
 - obturator nerve injury
- early post-op
 - atelectasis
 - delayed bleed
 - urine leak
 - vaginal leak
 - PE (2%)
 - wound infection
 - bowel anast leak
 - pneumonia
 - MI
 - DVT
- delayed post-op
 - bowel obstruction (4-10%)
 - ED
 - incontinence (more M)
 - obstruction (more F)
 - wound dehiscence/hernia
 - anast strictures (3%)
 - UTIs/pyelo
 - metabolic disorders
 - fistula
 - conduit stones
 - renal stones
 - stomal issues

SIMPLE CYSTECTOMY

What are the indications for a simple cystectomy? }}} “RIP & INFECT”

- Radiation cystitis (refractory)
- Incontinence (severe & refractory to other treatment)
- Pyocystic
- IC (refractory)
- Neurogenic bladder
- Fistula (large & refractory)
- Extenteration (as part of treatment of other pelvic malignant tumours)
- Cyclophosphamide cystitis (refractory)
- Trauma to urethra (severe)

What are the complications of urinary diversion without cystectomy?

- hemorrhage
- sepsis
- pain
- feelings of incomplete emptying
- fistulae
- pyocystis
- development of bladder cancer

➔ **secondary cystectomy needed in 10-20%**

Describe the main steps in a secondary simple cystectomy.

- ➔ in females } urethra, uterus, vagina spared
- ➔ in males } prostate, urethra, SVs spared
- lower midline incision
- develop space of Retzius
- distend bladder partially to facilitate dissection
- sweep peritoneum cephalad off bladder
- ➔ retrograde approach
 - ligate and divide superficial dorsal veins (on surface of prostate)
 - dissect bladder neck } identify ureteric orifices, SVs, vas
 - mobilize bladder off ampulla of vas and SVs
 - oversew prostate in 2 layers
 - continue to dissect bladder off rectum in retrograde fashion } Denonvillier's fascia
 - dissect lateral pedicle } superior & middle vesical branches of internal iliac
 - dissect off remaining peritoneum from superior aspect of bladder
- ➔ antegrade approach
 - dissect lateral pedicle } superior & middle vesical branches of internal iliac
 - dissect peritoneum off dome of bladder
 - develop plane between bladder and rectum
 - identify SVs and ampulla of vas
 - divide bladder neck
 - oversee prostate
- dissect off urachus
- irrigate wound
- JP drain

What are the potential complications after a simple cystectomy?

- ➔ similar to radical cystectomy
- ➔ complications often relate to the indication for cystectomy

PARTIAL CYSTECTOMY

What are the benefits of partial cystectomy?

- preservation of bladder
- preservation of sexual function
- complete pathologic staging of tumour
- pathologic staging of pelvic LNs

What are the ideal characteristics of a patient suitable for partial cystectomy?

- normally functioning bladder with good capacity
- first-time tumour occurrence with a solitary tumour
- tumour at dome that allows 1-2cm margin

What are the indications for partial cystectomy?

→ **only 5-20% of patients with muscle-invasive disease are suitable candidates**

→ “Don’t Do Partial Unless All Biopsies Safe”

- Dome TCC (solitary)
 - Diverticulum TCC (solitary) } high risk of mets (no detrusor → goes T1 to T3)
 - Pheochromocytoma (primary)
 - Urachal adenocarcinoma
 - Adjacent tumour invasion } colon, cervix, endometrial, ovarian Ca
 - Benign bladder disease (leiomyoma, fibroma, Hunner’s ulcer, symptomatic diverticulum, etc)
 - Sarcoma (primary) } osteosarcoma, leiomyosarcoma
- not considered definitive Rx for dome TCC
- survival rates of 25-55%
 - 5-10% TCC seeding rate reported
 - 40-80% TCC local recurrence rate for T2 disease

What are the contraindications to partial cystectomy? }}} “Can’t Mend Bladder HULC”

→ ABSOLUTE

- CIS elsewhere in bladder
- Multifocal tumours

→ RELATIVE

- Bladder neck or trigone involved
- High grade tumours
- Ureteral reimplantation required
- Lymphadenopathy
- Capacity issues (poorly functioning bladders)

What is the recommendation for high-risk patients that plan to undergo partial cystectomy?

- “high risk” } high grade, diverticular, large tumours
- multimodal approach recommended by some
 - neoadjuvant chemo +/- Rads
 - others have advocated the use of pre-op intravesical chemo
 - MMC

Describe the main steps of a partial cystectomy.

- cystoscopy may aid in intra-operative delineation of tumour location
- explore peritoneal cavity for mets
- identify, ligate, divide urachus (median umbilical ligament) below umbilicus
- develop space of Retzius
- dissect peritoneum off bladder laterally } if adherent to tumour, take with specimen
- mobilize bladder so adequate margin of non-involved bladder wall is available
 - fill bladder with sterile water to facilitate dissection
- pack off all other tissue in pelvis to avoid spillage seeding
- incise lateral bladder wall to expose tumour for inspection
- ligation of superior vesical artery on ipsilateral side of tumour often needed
- dissect out tumour with ~2cm margin
- stay sutures placed on resection margin to facilitate dissection
- send frozen-section margin from both lateral aspects of remaining bladder wall
- close bladder wall in 2 layers
- test closure by filling bladder via catheter } S/P not placed due to risk of seeding along tract
- place JP

What are some potential complications of a partial cystectomy?

- urinary leakage is primary complication } usually managed by prolonged catheter drainage
- voiding dysfunction if large portion of bladder has been removed
- wound infection
- hernia
- recurrent disease } local recurrence, seeding, unknown multifocality

What is the recommended follow-up after partial cystectomy?

- cysto + cytology q3months for at least 2yrs
- regular CT abdo/pelvis (q1yr)
- **local recurrence rates are from 40-80%**

Small Bowel

How long is the small bowel?

- approximately 22 feet } duodenum largest diameter
 - blood supply from SMA
 - 2/5 jejunum } larger diameter
 - } usually single arterial arcades (large vessels)
 - } thin mesentery
 - 3/5 ileum } smaller diameter
 - } multiple arterial arcades (small vessels)
 - } thick mesentery
- ~15cm of small bowel can survive lateral to a straight vessel that enters bowel
- don't clean off mesentery more than 8cm

Which segments of small bowel should be avoided in radiated patients?

→ **2 segments of small bowel may lie within pelvis**

- a) last 2 inches of terminal ileum
- b) 5 feet of jejunum that starts ~6ft from ligament of Treitz

Colon

Which segments of colon are free within the peritoneum?

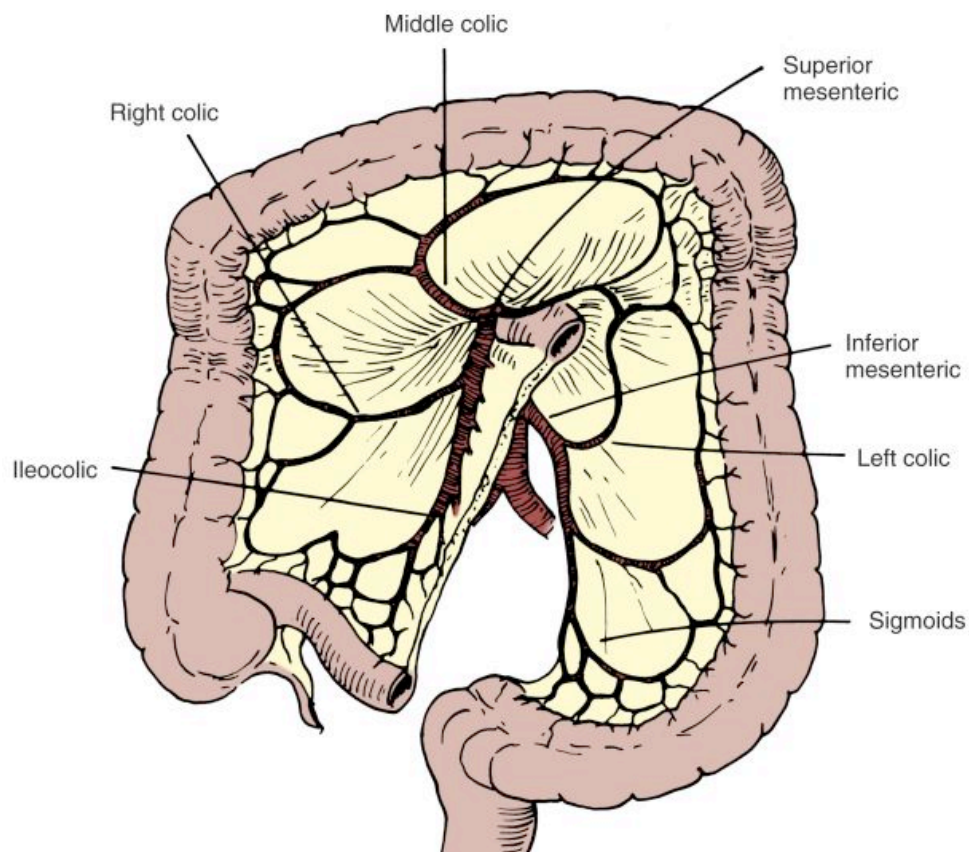
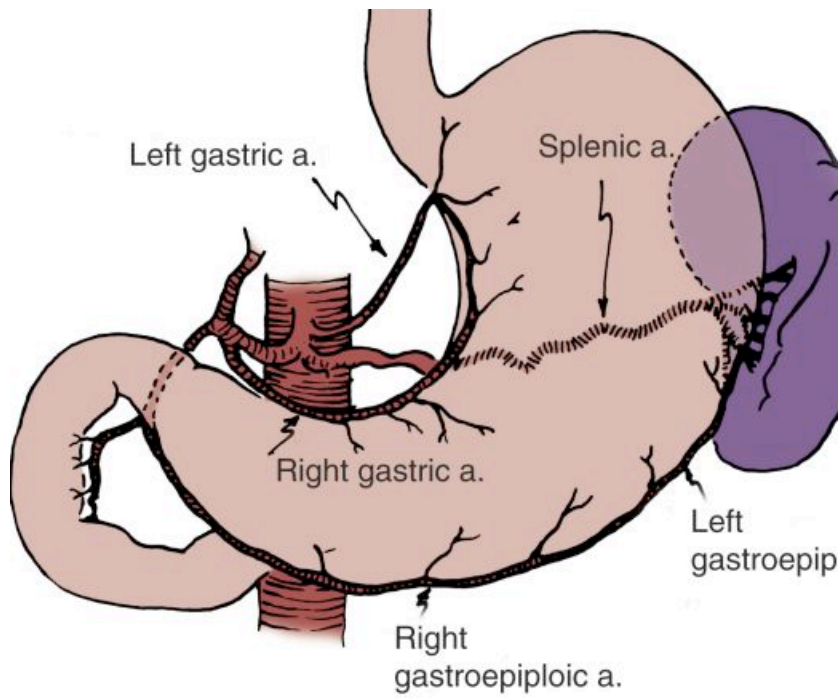
- cecum } usually fixed, by bands, to the retroperitoneum but on occasion is free
- transverse colon } FREE
 - } attached to stomach by gastrocolic omentum
- sigmoid colon } often FREE
- upper rectosigmoid } often FREE

What is the blood supply to the colon?

- SMA } ileocolic a. → terminal ileum (last 6 inches) and cecum
 - } right colic a. → cecum and ascending colon
 - } middle colic a. → transverse colon
 - IMA } left colic a. → descending colon
 - } sigmoidal branches → rectosigmoid
 - last branch is superior hemorrhoidal a.
 - superior hemorrhoidal then anastomoses w/ middle hemorrhoidal (from internal iliac) & inferior hemorrhoidal (from internal pudendal)
 - middle sacral a. } comes off aorta directly → may supply posterior aspect of rectum
- most arteries anastomose w/ each other to form arc of Drummond } allows for significant mobilization of colon

Where are the 3 weak areas in the vascular supply to the colon?

- 1) **Sudeck's critical point (weakest)** } junction between sigmoid & superior rectal arteries
- 2) midpoint between middle colic & R colic (hepatic flexure)
- 3) midpoint between middle colic & L colic (splenic flexure)



SELECTING THE SEGMENT OF INTESTINE

What are the advantages & disadvantages of the different intestinal segments?

	ADVANTAGES	DISADVANTAGES
STOMACH	<ul style="list-style-type: none">- less permeable to urinary solutes- has net excretion of H⁺ and CL⁻- produces less mucus- acidic urine produces less stomal skin irritation- rarely have lyte abN'ties if renal function is normal- lower incidence of bacteriuria- avoids adhesions which are more common in lower abdomen	<ul style="list-style-type: none">- can occasionally get severe hypoNa hypoCL hypoK MET <u>ALKALOSIS</u>- 10% incidence of obstruction- elevated gastrin levels a risk for major intestinal ulcers (PUD)- decreases stomach volume- high complications of gastric reconstruction (Billroth I)- hematuria-dysuria syndrome
JEJUNUM		<ul style="list-style-type: none">- severe electrolyte abN'ties such as hypoNa hypoCL <u>hyperK</u> MET ACIDOSIS- Fe deficiency- Ca deficiency
ILEUM	<ul style="list-style-type: none">- mobile- small diameter- constant blood supply	<ul style="list-style-type: none">- can result in anemia (Vit B12 def)- diarrhea (lack of bile salt reabsorption)- fat malabsorption (Vit A, D, E, K)- sometimes has excessive mesentery or very short mesentery- obstruction (10%) more common cf colon- <u>hyperCl</u> hypoK MET ACIDOSIS (~15%)
COLON	<ul style="list-style-type: none">- easily mobilized- upper colon safe to use even after pelvic RADs- fewer nutritional problems- lower incidence of bowel obstruction (4%)- easier to make anti-reflux anast. via submucosal tunnel	<ul style="list-style-type: none">- if ileocecal valve used can result in diarrhea, from bacterial colonization of ileum resulting in abN absorption & fluid loss- <u>hyperCl</u> hypoK MET ACIDOSIS (hypoK is more common w/ colon cf ileum)

What are some potential complications of using STOMACH for urinary diversion?

- usually requires Billroth I reconstruction (for sure when portion of antrum is used)
- early complications
 - gastric retention (atony or anastomotic edema)
 - hemorrhage (anastomotic site most common)
 - hiccups (gastric distension)
 - pancreatitis
 - duodenal leakage
- late complications
 - dumping syndrome
 - steatorrhea
 - small stomach syndrome
 - increased intestinal transit time
 - bilious vomiting
 - afferent loop syndrome
 - hypoproteinemia
 - anemia (Fe deficiency or megaloblastic)
 - bowel obstruction
 - bowel anastomotic leaks

BOWEL PREP

What is the classic teaching about bowel prep prior to intestinal surgery?

- lower wound infection rates
- lower incidence of intraperitoneal abscesses
- lower rate of anastomotic dehiscence
- decreased incidence of anastomotic leak
- infectious complications after radical cystectomy from fecal contamination occur in ~5-10%
- *** questionable ... Gen Sx rarely, if ever, do pre-op bowel preps ... BUT we get into urinary tract ***

What types of bowel prep are there?

- 1) mechanical } reduces fecal load (**lower total # of bacteria BUT NOT lower concentⁿ**)
 - eg GoLYTELY (4L in adults, 25 cc/kg/hr in kids)
 - } conventional (CF + 45cc Fleet phosphasoda 2d pre-op & 30cc 1d pre-op)
 - VS whole-gut (NG + 10L Ringer's 1d pre-op)
- 2) antibiotic } reduces bacterial counts
 - **highest usually in descending colon ($10^{10} - 10^{12}$ organisms/g feces)**
 - **lowest in jejunum ($10-10^5$ organisms/g feces)**
 - eg 1g kanamycin qid for 3 days
 - eg 1g neomycin qid for 2 days + 750mg flagyl qid for 2days

What are the advantages & disadvantages of whole-gut irrigation mechanical prep?

- ADVANTAGES } dietary freedom until 1d pre-op
 - } short prep time
 - } no enema needed
- DISADVANTAGES } hard on patient
 - } can cause fluid overload (rare)

What are the contraindications to whole-gut irrigation?

- unstable CV system
- CHF
- cirrhosis
- bowel obstruction
- severe renal disease

What are the contraindications to Fleet Phospha-Soda mechanical prep (45cc Na PO₄ bid day before Sx)?

- 1) renal insufficiency
- 2) hyperPO₄
- 3) hypoCa

What is the newer data on bowel prep prior to intestinal surgery?

- **meta-analysis of RCTs shows NO benefit of bowel prep for bowel sx** (Guenaga et al, '05)
→ may in fact increase rate of anastomotic leakage & wound complications

What are the disadvantages of antibiotic prep?

- **likely does reduce post-op complications BUT ...**
- higher incidence of post-op diarrhea
- higher incidence of C diff. colitis
- theoretical increase in incidence of tumour implantation at suture line
- stomatitis and thrush more common
- malabsorption of protein, carbs, and fat

What is the role of peri-op IV Abx?

- effective when given 1-2 hours before start of surgery (amp, gent, flagyl OR amp, ceftriaxone, flagyl)
- **essential to have anaerobic coverage** } **most effective at decreasing complications**

How does pseudomembranous colitis usually present?

- due to *C. diff* overgrowth } normal flora that usually inhibits *C. diff* is destroyed by ABx
 } toxin produces diffuse inflammatory response
- abdo pain + diarrhea } **diarrhea is KEY**
- usually NO fever or chills
- very high WBC count
- patients may get septic } toxic megacolon → ~20% mortality rate

What is the treatment of C diff enterocolitis?

- stop other ABx
- flagyl } can be given po AND iv
- vancomycin } can be given ONLY PO
- if toxic megacolon } subtotal colectomy is lifesaving procedure required

INTESTINAL ANASTOMOSES

What are the fundamental principles of intestinal anastomoses?

- **most common cause of M&M in early post-op period after urinary diversion using bowel relates to complications involving the bowel**
- **75% of mortality in post-op period was related to bowel**
- 1) adequate exposure → mobilize adequate length of bowel
 - clear mesenteric fat from bowel to ensure good serosal apposition
- 2) maintain good blood supply to ends of bowel → avoid tension on anastomosis
 - avoid excessive dissection or mobilization of bowel
 - avoid cautery when possible
- 3) prevent local spillage of enteric contents → towel off anastomotic site
 - milk fecal contents away from anastomosis
 - irrigate segment to be used for diversion
- 4) ensure accurate apposition of serosa to serosa → watertight, tension-free anastomosis
- 5) avoid tissue strangulation → appose don't necrose
- 6) realign mesentery of 2 segments of bowel to be rejoined → avoid twisted bowel
 - prevent internal hernias

Sutured Anastomoses

What are the different methods of performing sutured bowel anastomoses?

- 1) 2-layer enteroenterostomy
 - 3-0 silk placed on mesenteric & antimesenteric border
 - 3-0 silk seromuscular sutures placed on posterior wall
 - 3-0 chromic placed full-thickness (incl. mucosa) on posterior wall then run laterally to ends & converted to a Connell suture on anterior wall (full thickness)
 - 3-0 silk seromuscular suture placed on anterior suture line
 - **most secure anastomosis } used for suboptimal anast's & for Billroth 1**
- 2) single layer enteroenterostomy
 - interrupted 3-0 silks started on mesenteric border finishing on anti-mesenteric side
 - more serosa than mucosa with each bite
 - ensure to invert suture line and appose serosa
 - **low complication rate (<1%)**
- 3) end-to-side ileocolic anastomosis
 - close off transected end of colon like proximal end of conduit (Connell stitch + baseball stitch on top)
 - ileal serosa sutured with interrupted 3-0 silk to colonic serosa 2mm below a taenia
 - taenia is incised length of ileal diameter
 - ileum is anastomosed to colon via 2-layer closure (seromuscular and full thickness)
- 4) ileocolonic end-to-end anastomosis
 - 3-0 silk sutures placed on mesenteric & anti-mesenteric borders
 - spatulate smaller ileum so diameters of each lumen are equivalent
 - 2-layer closure (seromuscular + full thickness)

Stapled Anastomoses

What are the theoretical benefits of a stapled bowel anastomosis?

- better blood supply to healing margin
- reduced tissue manipulation
- minimal edema
- uniformity of suture placement
- wider lumen
- easier & faster
- decreased length of post-op ileus
- **similar complication rates } leak and fistula rate of ~3%**
- **for end-to-side ileocolic anastomosis, stapled is better than hand-sewn**
 - **circular stapler makes wider lumen**

Which staplers are used for bowel anastomoses?

- type } linear eg TA
- } anastomotic eg GIA or circular
- length } depends on how long suture line needs to be
- height } usually need 1.5mm closed height for bowel (open 3.5mm)
- diameter } depends on diameter of tissue to be stapled

What are the different types of stapled bowel anastomoses?

- 1) ileocolonic end-to-side } circular stapler (post, anvil, and purse-string sutures)
 - } 3-0 silk seromuscular sutures reinforce circumference of anastomotic line
 - } close transected end of colon via TA stapler
- 2) end-to-end bowel anastomosis } pant-leg with pin-silk stay sutures
 - } GIA along antimesenteric border
 - } TA along open end of bowel

Laparoscopic Anastomoses

How are bowel anastomoses performed laparoscopically?

- 1) entirely intracorporeally } advanced
- 2) intracorporeal bowel mobilization + extracorporeal anastomosis after bowel exteriorization

Post-op Care

What are the factors predictive of anastomotic leakage?

- poor blood supply } iatrogenic, radiation, etc
- local sepsis induced by fecal spillage
- irradiated bowel
- malnourished patient
- drains placed on anastomosis

When is the ideal time to feed patients?

- small bowel activity returns within hours
- stomach activity returns within 24hrs
- CF with resolution of paralytic ileus } DAT if tolerating CF
- TPN started post-op if } a) severely impaired nutrition pre-op
- b) prolonged paralytic ileus (>7-10days NPO)
- c) complications that delay feeding
- TPN started immediately post-op if any of these complications are anticipated

What are the arguments for and against NG tube use?

- FOR } studies show less N/V, less abdo distension
- } studies show less wound complications
- } allows for ice chips (comfort)
- AGAINST } studies show **no difference in major intestinal complications**
- } studies show earlier return of bowel function without NG
- } some studies show fewer pulmonary complications
- push toward not using NG or short course of NG
- healthy patients likely don't need it

Complications of Intestinal Anastomoses

What are the potential complications of the BOWEL ANASTOMOSES?

- anastomotic leak (2%)
- bowel obstruction or anastomotic stenosis (4%) } bowel obstruction more common with
- stomach/ileum (10%) cf colon (5%)
- } early vs late
- fistulae (5%) } fecal or urinary → usually occur in first few weeks
- } can be complicated by sepsis (2% mortality)
- abdo/pelvic abscesses
- pseudo-obstruction of colon (Ogilvie's) } usually occurs within first 3 days
- sepsis
- hemorrhage (1%) } more common when stomach used (anastomotic bleeders or ulcers)
- wound infections & wound dehiscences (5%)

What are some strategies to reduce post-op bowel obstruction?

- use non-radiated bowel
- perform anastomosis with well-vascularized bowel
- close all defects in mesentery, etc
- re-peritonealize isolated segment
- decompress GI tract for adequate time
- place omentum over anastomosis
- reconstitute pelvic floor after exenterative surgery

What are the causes of anastomotic stenosis?

- 1) early post-op } usually edema or technical issue
- 2) delayed } ischemia or peri-enteric infection

What is the management of Ogilvie's syndrome?

- ensure normal electrolytes, etc
- stop meds that may precipitate or exacerbate (narcotics, anti-cholinergics)
- endoscopic decompression (scope, rectal tube, etc)
- neostigmine } watch for reflex bradycardia (keep atropine on hand)
- emergency cecostomy tube

Complications of Isolated Intestinal segment

What are the potential complications of the ISOLATED BOWEL SEGMENT?

- 1) bowel stricture } usually a late complication
 - } mainly seen in ileal conduits (have been described in ileal ureters)
 - } ? related to lymphoid depletion of bowel exposed to urine
 - persistent infection results in fibrosis & stricture
 - } may also involve encroachment by hypertrophied mesenteric LNs
- 2) elongation of segment } can be due to distal obstruction (conduits, ileal ureters) or failure to catheterize frequently (continent diversions)
 - } can lead to volvulus, renal deterioration from increased pressure

Abdominal Stomas

What types of stomas are used?

- 1) flush stomas } preferred for continent diversions that are catheterized
 - } higher incidence of stomal stenosis (epithelial overgrowth)
- 2) protruding stomas } preferred for incontinent diversions with appliance
 - } lower incidence of stomal stenosis from epithelial overgrowth
 - } fewer peristomal skin problems
 - } end stoma vs loop end ileostomy (Turnbull)
 - Turnbull better for obese pt w/ thick abdo wall & short mesentery
 - rod for 7days max
 - proximal loop edge rosebudded
 - stomal stenosis uncommon but parastomal hernias more common with loop end ileostomy

What are the basic principles of siting a stoma?

- place it over rectus muscle at least 5cm from incision site
- place away from skin fold, scar, umbilicus, belt lines
- avoid previously radiated fields

Complications of stomas

What are the potential complications of an intestinal STOMA?

→ MOST COMMON PROBLEM in POST-OP PERIOD AFTER URINARY DIVERSION

- bowel necrosis
- bleeding } if massive, usually from varices (Rx – embolization)
- dermatitis } from alkaline urine
- parastomal skin lesions
- parastomal hernia } 1-4% in end stomas and 4-20% in loop stomas
- prolapse
- obstruction
- stomal retraction } most severe situation is muco-cutaneous separation
- stomal stenosis } 20-25% of ileal conduits, 10-20% of colon conduits
 - } less common for loop stomas & most common with flush stomas (~50%)
 - umbilical >>> abdo wall
- poor appliance fit
- poor siting of stoma } can't see because in crease, under skin roll, etc

How can one classify parastomal skin lesions? } “PIE”

- 1) **P**seudoverrucous } wartlike
- 2) **I**rritative } hypopigmented, hyperpigmented, and skin atrophy
- 3) **E**rythematous erosive } macular lesions, scaling, and loss of epidermis

What are some ways to reduce stomal complications?

- proper construction of stoma
- maintain acidic urine
- properly fitting appliance
- f/u with enterostomal therapist
- non-irritative stomal adhesives



→ Stomal necrosis



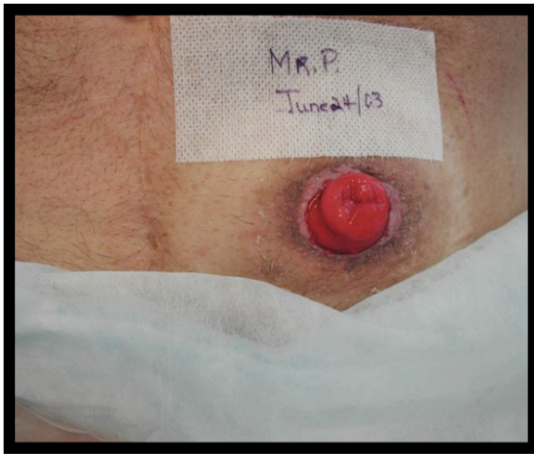
→ Stomal retraction with muco-cutaneous separation



→ Irritant Contact dermatitis



→ Parastomal candidiasis



→ Parastomal skin lesion (pseudoverrucous form)



→ Parastomal hernia

URETEROINTESTINAL ANASTOMOSES

What are the main causes of upper tract deterioration after ureterointestinal anastomoses?

- 1) lack of ureteral motility
- 2) infection
- 3) stones
- 4) anastomotic obstruction/stricture (least common)

Are non-refluxing anastomoses better than refluxing anastomoses?

- conflicting data on whether refluxing anastomoses are assoc'd w/ ↑'d upper tract deterioration
→ likely YES, if in setting of impaired ureteral peristalsis + infection/obstruction
- **definitely higher rate of anastomotic strictures with non-refluxing anastomoses**
- no difference in bacterial colonization of renal pelvis } conduit pressures are not transmitted to pelvis

What are the basic principles of ureterointestinal anastomoses?

- mobilize only as much ureter as needed } tension-free without redundancy
- don't strip ureter of its peri-adventitial tissue } blood supply
- use fine absorbable sutures to make water-tight, mucosa-to-mucosa anastomosis
- fix bowel to abdo cavity when possible, adjacent to site of ureterointestinal anastomosis
- retroperitonealize anastomosis when possible, or cover with omental flap
- stent the anastomosis
- JP drain

Ureterocolonic Anastomoses

Describe the different types of uretero-COLONIC anastomoses?

→ NON-REFLUXING

1) Leadbetter-Clarke } extra-colonic

- inject submucosal tissue of colon with saline
- linear incision in taenia and flap of taenia raised
- small button of mucosa removed and anastomosis made
- seromuscular layer sutured over ureter (tunneled)

→ HIGH stricture rate (14%)

2) Strickler } extra-colonic

- small linear incision made in taenia
- dissect out 3-4cm submucosal tunnel laterally
- make small hole in serosa & pull ureter through to incision over taenia
- button of mucosa excised & anastomosis made
- adventitial suture placed to secure ureter to colon serosa

→ HIGH stricture rate (14%)

3) Pagano } extra-colonic

- linear incision made in taenia for 4-5cm in length
- dissect submucosa from mucosa laterally on both sides
- draw ureters into submucosal tunnel distally through small hole in serosa
- make anastomosis
- close taenia & incorporate mucosa in midline to separate ureters in submucosa

} anterior version of GOODWIN

→ LOW COMPLICATION rate

→ LOWEST stricture rate (6%)

4) Goodwin } trans-colonic

- colon opened on anterior surface
- small rent made in mucosa, which is raised from submucosa beneath to create a tunnel running laterally
- run tunnel 3-4cm then exit serosal wall
- ureter grasped and pulled into tunnel through to lumen of colon
- anastomosis made from within the colon (make sure to include some muscularis for strength)
- suture adventitia of ureter to serosa of bowel

} posterior version of PAGANO

} colonic version of LE DUC ureteroenteric anastomosis

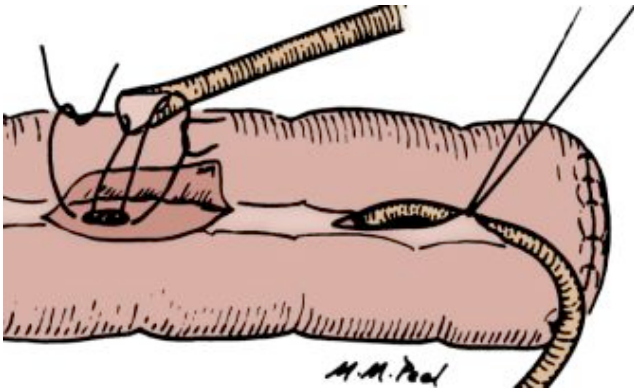
→ limited data

→ REFLUXING

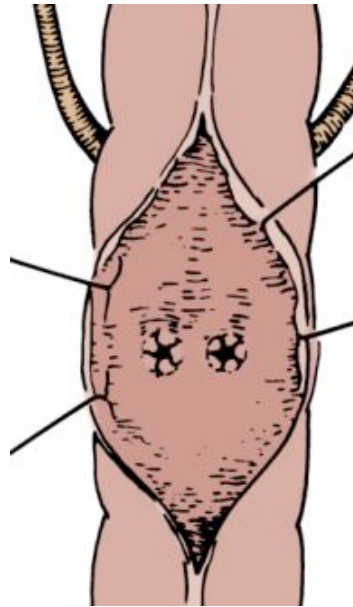
1) Cordonnier & Nesbit } direct refluxing anastomosis

} not preferred for ureterosigmoidostomies

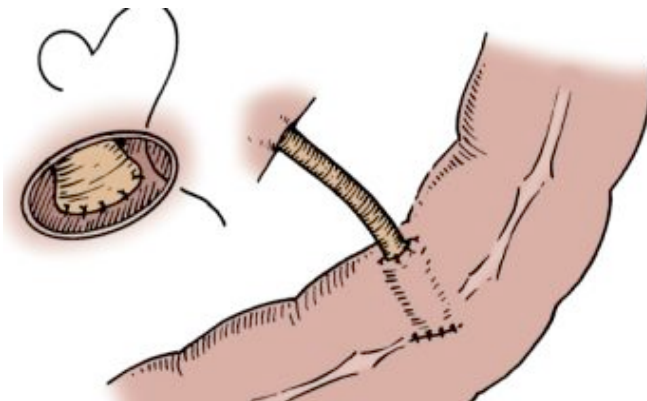
} colonic version of BRICKER ureteroenteric anastomosis



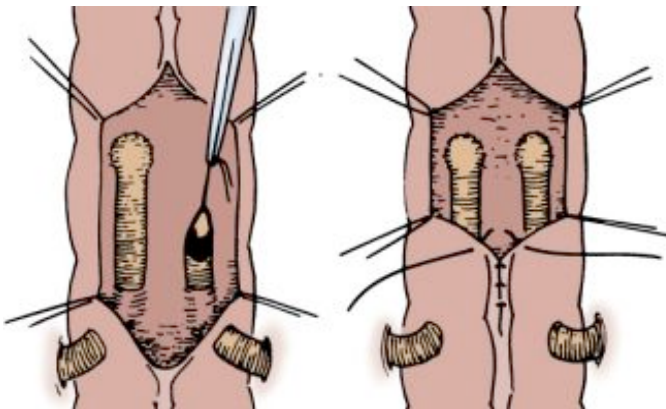
→ LEADBETTER-CLARKE



→ GOODWIN



→ STRICKLER



→ PAGANO (lowest complication rate, lowest stricture rate)

Ureteroenteric Anastomoses

Describe the different types of uretero-ENTERIC anastomoses? } “BW SLUT HAMMOCK”

→ Bricker, Wallace

→ Split nipple, Le Duc, Ureteral compression, Tunneled, Hammock

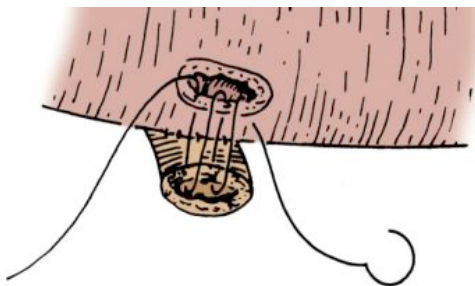
1) REFLUXING

- a) **Bricker** } end-to-side (aka Leadbetter)
 } full-thickness ureter to full-thickness small bowel anastomosis
 → simple with LOW COMPLICATION rate
 → LOW stricture rate (6%)

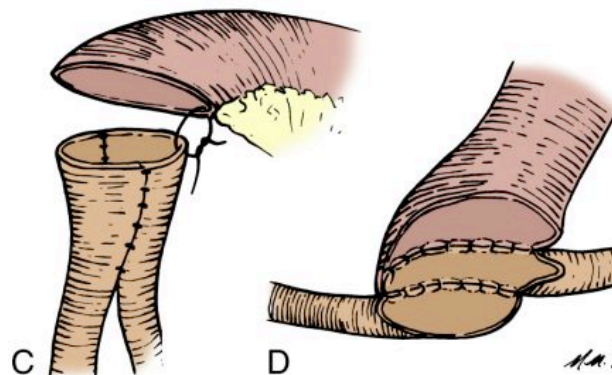
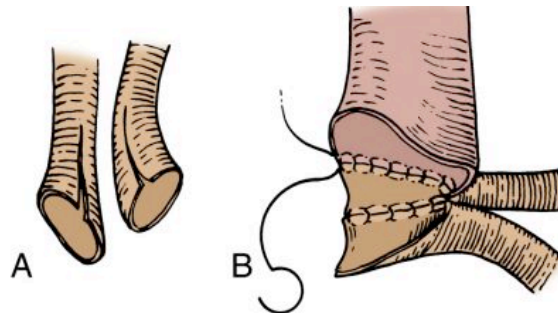
- b) **Wallace** } end-to-end
 } 3 different configurations used
 i. ends of both ureters sutured together and this composite is then
 sutured to end of bowel
 ii. ureters pant-legged then sutured to end of bowel
 ii. head-to-tail anastomosis of ureteric ends, which is then sutured
 to end of bowel

→ contraindicated if extensive CIS or high likelihood of recurrence in one ureter

→ LOWEST COMPLICATION RATE of any ureterointestinal anastomosis (stricture rate 3%, leak rate 2%)



→ BRICKER



→ WALLACE

2) NON-REFLUXING

- a) **Griffiths Split-nipple** } 5mm longitudinal incision made in ureter and ureter is then intussuscepted
 } end of intussuscepted ureter is secured to adventitia
 } nipple made twice as long as width
 } anastomose ureter into bowel w/ nipple protruding into lumen of bowel

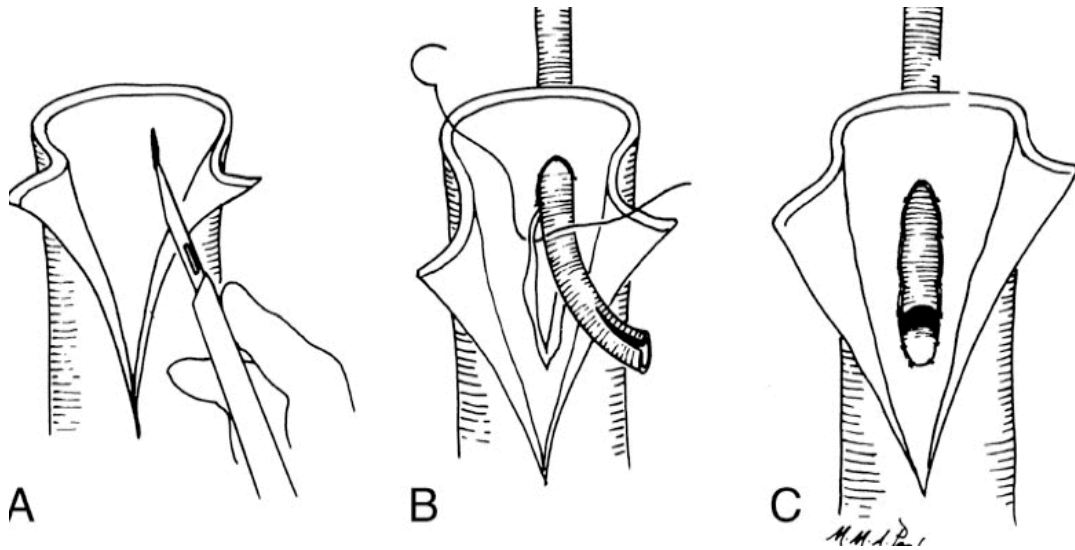
→ **HIGH reflux rate (15%)**

- b) **Le Duc** } transenteric
 - open small bowel 4-5cm
 - make longitudinal rent in mucosa and raise mucosa from submucosa
 - make hole in serosa at distal end of rent and pull ureter through to a point ≥ 2 cm from cut end of bowel to allow closure of bowel
 - ureter is spatulated and anastomosis made
 - ureteric adventitia sutured to bowel serosa

→ **LOWEST stricture rate with modification (3% vs previous 15%)**

→ **HIGHEST success rate for anti-reflux**

→ ileal version of GOODWIN ureterocolonic anastomosis



→ LE DUC anti-reflux ureteroenteric anastomosis (without modification)

- c) **Ureteral compression by seromuscular layer ("Ghoneim")** } mainly for continent diversions with "W" configuration
 } ureters laid in troughs created by apposed bowel segments
 } anastomosis made at apex of "W" and seromuscular-mucosal layer closed over ureter anteriorly

→ **LOW reflux rate (3%)**

- d) **Tunneled anastomosis** } 3cm submucosal tunnel with 2 transverse incisions
 } small bowel version of STRICKLER (except no tenia)

→ **not used often so limited data**

- e) **Hammock** } ureters joined Wallace-style then implanted in nonrefluxing manner
 → **HIGH reflux rate (20%)**

Intestinal Anti-reflux Valves

Describe the different types of intestinal anti-reflux valves?

- ureters anastomosed using Bricker or Wallace
- end of bowel distal to anastomosis is used to create one-way valve
- **failure of valve or stenosis of anastomosis will affect both kidneys**
- 1) intussuscepted ileocecal valve } clean off mesentery from distal 8cm of terminal ileum
 - } isolate total of at least 13cm of ileum
 - } intussuscept 8cm segment of distal ileum into cecum over 22Fr catheter
 - } secure intussuscepted ileum to cecal wall circumferentially
 - can incise mucosa of intussuscepted ileum & mucosa of cecal wall then suture together to reduce chance of reduction

→ HIGH FAILURE RATE (nipple reduces)
- 2) intussuscepted ileal nipple valve } clean off mesentery from 8cm of ileum
 - } isolate total of ≥18cm of ileum (ensure ≥5cm of ileum w/ N mesentery on either side of cleared segment)
 - } open distal end of ileum and use Babcock clamp to then intussuscept cleared 8cm segment of ileum
 - } use GI stapler (w/o knife) to keep 5cm protruding nipple in place
 - remove some distal staples close to end of nipple
 - } incise mucosa of distal ileum & protruding segment and suture together to hold intussusception in place

→ 10% COMPLICATION RATE
(5% stones, 4% stenosis, and 1% prolapse)
→ T-pouch modification ↓'s complications (USC – Stein/Skinner)
- 3) ileal nipple valve placed into colon } clean off mesentery from distal 8cm of terminal ileum
 - } intussuscept distal 6cm of ileum to form nipple
 - } suture end of ileum to serosa of ileum to form stable 4-5cm nipple
 - } incise taenia of colon & suture serosa of nipple to colon serosa

→ SIMPLEST TYPE

Complications of Ureterointestinal Anastomoses

What are the potential complications of a URETEROINTESTINAL ANASTOMOSES?

- urine leakage (3-5%) } may lead to stricture formation
 - } ↓'d rate with soft stents
- stricture } occurs more often with anti-reflux techniques (more common in colon)
 - } can also occur away from anastomosis; most commonly on L
 - lowest with Wallace (refluxing small bowel) & Pagano (non-refluxing colon)
 - r/o recurrence of malignancy for late strictures
- urinary fistulae } usually occur in first 7-10days post-op (3-9%)
 - } ↓'d rates with use of soft stents
- reflux in anti-reflux anastomosis
- pyelo } more common in ileal conduits (10-20%) cf anti-reflux colon conduits (10%)
 - } sepsis can result and is a significant cause of morbidity and mortality
- renal failure } most common with ureterosigmoidostomies

What are the main causes of ureterointestinal anastomotic strictures?

- ischemia
- urine leak
- RADs
- infection

What are the management options for ureteroenteric anastomotic strictures?

- 1) endourologic surgery
 - **1st line therapy**
 - balloon dilation } not good for long strictures
 } poor overall long-term success rates → 5-15% 3yr success rate
 - electroincision endoureterotomy \
 - cautery wire balloon incision } ~50% long-term patency
 - laser endoureterotomy /
 - Hobbs rather than ureteric stent preferred } mucous plugging
 - **antegrade approach favoured for ureteroenteric/ureterocolonic strictures**
 - consider open for L-sided strictures } risk of hemorrhage from sigmoid mesentery
 } lower overall success rates on the L
- 2) open surgery
 - **2nd line therapy**
 - if enough ureteral length not available, may require additional segment of bowel to interpose between ureter and reservoir
 - success rates ~75% at 3yrs } lower success rates on the L
 - strictures >1cm more likely to recur

What are the factors that predict poor outcome for endourologic management of a stricture?

- early strictures (within 1yr of surgery)
- strictures >1.5cm
- left-sided strictures

What are the potential complications of urinary diversion?

Complications	Type of Diversion	Patients (Complications/N)	Incidence (%)
Bowel obstruction	Ileal conduit	124/1289	10
	Colon conduit	9/230	5
	Gastric conduit	2/21	10
	Continent diversion	2/250	4
Ureteral intestinal obstruction	Ileal conduit	90/1142	8
	Antireflux colon conduit	25/122	20
	Colon conduit	8/92	9
	Continent diversion	16/461	4
Urine leak	Ileal conduit	23/886	3
	Colon conduit	6/130	5
	Continent diversion	104/629	17
	Ileum	5/123	4
	Colon		
Stomal stenosis or hernia	Ileal conduit	196/806	24
	Colon conduit	45/227	20
	Continent diversion	28/310	9
Renal calculi	Ileal conduit	70/964	7
	Antireflux colon conduit	5/94	5
Pouch calculi	Continent diversion	42/317	13
Acidosis requiring treatment	Ileal conduit	46/296	16
	Antireflux colon conduit	5/94	5
	Gastric conduit	0/21	0
	Continent Diversion		
Pyelonephritis	Ileum	21/263	8
	Colon or colon-ileum	17/63	27
	Ileal conduit	132/1142	12
	Antireflux colon conduit	13/96	13
	Continent diversion	15/296	5
Renal deterioration	Ileal conduit	146/808	18
	Antireflux colon conduit	15/103	15

RENAL DETERIORATION

How common is renal deterioration in patients with previously N renal function?

- ileal conduits → 18%
→ 6% mortality due to renal failure
- non-refluxing colon conduits → 13%
- ureterosigmoidostomy → **highest rate of renal failure AND sepsis**
→ 10-20% mortality due to renal failure or sepsis

What amount of renal function is required to have a urinary diversion?

- depends on } type of bowel segment used
- } amount of bowel used
- } length of time urine is exposed to GI mucosa
→ kidneys deal w/ reabsorption of urinary solutes & prevent metabolic S/Es
- need more renal function for continent diversions than for short conduits
- **need at least GFR of 40 mL/min for continent diversions**
- **distal tubule function is also important, not just GFR**

Name the 5 aspects of renal function to be assessed before consideration of a urinary diversion.

- generally ok if creatinine level is $<180 \mu\text{mol/L}$ (or $<2\text{mg/dL}$) + no proteinuria
- 1) renal blood flow } **creatinine $<180 \mu\text{mol/L}$** is good measure (cytostatin C may be better)
- 2) GFR } **ok if GFR $>35\text{-}40\text{mL/min}$**
- 3) glomerular permeability } **ok if minimal proteinuria**
- 4) tubule transport/ability to acidify } **ok if urine pH ≤ 5.8** after acid (NH_4Cl) loading
- 5) concentration & dilution } **ok if urine osmolality is $\geq 600 \text{ mOsm/kg}$** after water deprivation

URINARY DIVERSION

What are the goals of urinary diversion?

- 1) adequate capacity, low-pressure reservoir
- 2) no fecal contamination
- 3) complete and voluntary emptying
- 4) no ureteral reflux if possible
- 5) no electrolyte absorption if possible

What are the different options for urinary diversion after radical cystectomy?

- incontinent
 - conduit } eg ileal, colon, jejunal
- continent
 - neobladders } eg Studer ileal neobladder, Mainz pouch, T pouch ileal neobladder, Ghoneim, Le Bag ileocolic pouch, Kock ileal neobladder, Camey II
 - cutaneous reservoirs } eg Indiana pouch, Mainz I, Double T pouch, Kock pouch
 - rectal diversions } eg ureterosigmoidostomy, Mainz II, rectal bladder, folded rectosigmoid

What are the contraindications to the different urinary diversions?

- ileal conduit contraindications } “SIR”
 - short bowel syndrome
 - IBD of small bowel
 - radiated ileum
- colon conduit contraindications } “ID +”
 - IBD of colon
 - severe chronic diarrhea
 - sigmoid diverticulitis for sigmoid conduit
 - extensive pelvic RADs for sigmoid conduit
- general contraindications to diversions other than conduit
 - creatinine >180
 - GFR <35-40
 - proteinuria
 - unable to acidify urine to pH <5.8
 - unable to concentrate urine to osmolality >600
- continent cutaneous reservoirs & neobladders } “RUM RAIDS Liver”
 - +ve urethral margin (neobladder)
 - known urethral TCC (neobladder)
 - extensive RADs
 - IBD
 - dexterity issues (unable to perform CIC eg MR, quadraplegic, morbidly obese, etc)
 - short length of bowel
 - liver failure
- continent rectal reservoirs } “RURAL Diverticulitis”
 - extensive pelvic RADs
 - dilated ureters
 - incompetent anal sphincter
 - liver failure
 - colorectal disease (eg IBD, diverticulitis)

What are the indications for a urinary conduit?

- 1) after cystectomy } cancer
 - } refractory hematuria (eg hemorrhagic cystitis)
- 2) before renal Tx in patient with diseased bladder that can't receive transplant ureter
- 3) poor compliance with upper tract deterioration
- 4) inadequate storage with total urinary incontinence

Ileal Conduit

What are the advantages of an ileal conduit?

- simplest type of conduit
- associated with fewest intra-op and immediate post-op complications

What are the contraindications to an ileal conduit? }} “SIR”

- **S**hort bowel syndrome
- **I**BD of the small bowel
- **R**adiated ileum (extensive RADs)

What are the general steps/principles of an ileal conduit?

- 10-15cm segment taken approximately 10-15cm from ileocecal valve
- identify major arcade feeding segment of bowel
- base of mesentery should be as wide as possible and the mesenteric windows not excessive
- bowel transected so antimesenteric portion is shorter than mesenteric portion
- triangular piece of bowel is removed (bowel with mesentery)
- **isolated ileal segment placed caudad & bowel re-anastomosed cephalad**
- ureters identified caudad to iliac vessels and dissected cephalad
- ureteral-ileal anastomosis made } can even make anastomosis of ileal conduit to renal pelvis

What are the potential complications of an ileal conduit?

→ early (all ~2-3%, unless stated otherwise)

- urine leak
- bowel leak
- sepsis
- wound infection (7%)
- wound dehiscence
- GI bleed
- prolonged ileus (6%)
- bowel obstruction

→ late

- renal failure (~20% new renal deterioration, 7% require hemodialysis)
- HTN
- acute pyelo (20%)
- sepsis
- conduit/stoma bleed (10%) } if severe may be due to cirrhosis and varices
- bowel obstruction (10%)
- ureteral obstruction (4-8%)
- parastomal hernia
- stomal stenosis
- stomal skin lesions } irritative, erosive, pseudoverrucous
- stones (7%)
- volvulus (7%)
- **hyperCl, hypoK METABOLIC ACIDOSIS (13%)**
Rx → NaHCO₃ or K citrate for acidosis +/- K supplements + chlorpromazine

Jejunal Conduit

What are the advantages of a jejunal conduit?

→ **10-15cm segment isolated 15-25cm from ligament of Treitz with LUQ stoma**

- avoids irradiated bowel & ureter
- avoids severe adhesions of ileum
- larger diameter of small bowel & long mesentery
- absence of colon +/- IBD of distal small bowel

What are the contraindications to a jejunal conduit?

- **the presence of another acceptable segment of small bowel**
- severe bowel nutritional disorders

What are the potential complications of a jejunal conduit?

→ early

- urine leak (15%)
- wound dehiscence (5%)
- GI bleed (5%)
- enteric fistula (2%)

→ late

- renal failure
- acute pyelo (10%), sepsis
- stomal stenosis (7%)
- bowel obstruction (7%)
- ureteral stricture (12%)
- stones (12%)
- parastomal hernia
- **hypoCl, hyperK, hypoNa METABOLIC ACIDOSIS (30%)**
Rx → Na bicarb, HCTZ

Colon Conduit

What are the different types of colon conduits?

	ADVANTAGES	CONTRAINDICATIONS
ileocecal	<ul style="list-style-type: none">- provides colon for the stoma- can provide long segment of ileum if ureters are short- allows for non-refluxing conduit	<ul style="list-style-type: none">- IBD of colon- severe chronic diarrhea
transverse	<ul style="list-style-type: none">- non-irradiated colon if hx of pelvic RADs- good if intestinal pyelostomy req'd	<ul style="list-style-type: none">- IBD of colon- severe chronic diarrhea
sigmoid	<ul style="list-style-type: none">- good for pelvic exent + colostomy (no bowel anastomosis req'd)- allows for non-refluxing reimplantation- good if L-sided stoma needed	<ul style="list-style-type: none">- IBD of colon- severe chronic diarrhea- sigmoid diverticulitis- if internal iliacs have been ligated and rectum in situ- extensive pelvic RADs

What are the general steps/principles of a colon conduit?

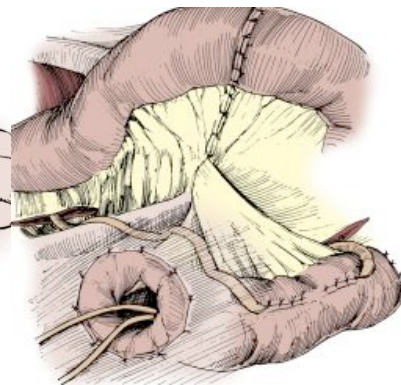
- 1) ileocecal
 - isolate ileocecal conduit on **ileocecal artery** (last branches of SMA)
 - bowel reanastomosis placed cephalad to isolated segment
 - ileocecal valve reinforced to prevent reflux
 - stoma placed in RLQ
- 2) transverse
 - isolate segment on **middle colic artery** (can also use R colic)
 - usually 15cm length is sufficient
 - mobilize gastrocolic ligament and hepatic & splenic flexures
 - colo-colostomy is made on cephalad side of isolated segment
 - if colopyelostomy to be performed, segment is placed cephalad to anastomosis
 - stoma usually placed in RUQ
- 3) sigmoid
 - isolate segment on **sigmoid vessels**
 - mobilize by incising peritoneal attachments and white line of Toldt
 - conduit placed lateral to bowel anastomosis
 - stoma placed in LLQ

What are the potential complications of a colon conduit?

- has **lower incidence of pyelonephritis & renal deterioration** than small bowel
- early
 - urine leak } **lowest with sigmoid conduit (1%)**, others similar (~7%)
 - wound infection/dehiscence } lowest with sigmoid conduit (1%)
 - bowel obstruction } **least common with sigmoid conduit** in early period
- late
 - acute pyelo } **least common with sigmoid conduit (7%)**, others similar (10-15%)
 - bowel obstruction } **least common with transverse conduit** in late period (4-5%)
 - stones } **most common with transverse colon (10%)**, others similar (5%)
 - ureteral stricture } **most common with transverse conduit (17%)**, others <10%
 - stomal stenosis/hernia } stenosis/hernia similar with all (2-3%),
 - chronic diarrhea
 - renal deterioration/failure (15%)



→ TRANSVERSE COLON CONDUIT



→ SIGMOID CONDUIT

Ileal Vesicostomy

What are the advantages of an ileal vesicostomy?

→ “ileal chimney”

- ideal for SCI patients or those w/ significant neurological disease (eg. for DESD & neurogenic bladder)
- results in low-pressure reservoir
- allows for conversion to normal anatomy at a later date
- easier to care for

What are the general steps/principles of an ileal vesicostomy?

- spatulate isolated ileal segment
- perform generous transverse cystotomy
- rosebud stoma

What are the potential complications of an ileal vesicostomy?

- urethral incontinence (20%) } mainly in women
- stomal stenosis
- bladder stones
- renal stones
- urine leak
- bowel obstruction
- acute pyelo

Metabolic Complications

→ G-DIVERSIONS

- 1) Growth retardation } bone growth & bone healing affected
 } long term diversions place patient at higher risk of fractures and complications after orthopedic surgery
- 2) Drug metabolism abN'ities } for drugs absorbed by GI tract & excreted unchanged renally
 } eg Dilantin, chemo (MTX), certain ABx (nitrofurantoin)
Rx → alkalinization + drainage during chemo
- 3) Infections (persistent, recurrent) } increased incidence of bacteriuria, bacteremia, sepsis
 } more common after colostomy vs ileostomy
 } renal deterioration more common with pure *Proteus* or *Pseudomonas* bacteriuria
 → may warrant Rx even if asymptomatic
- 4) Vitamin B12 deficiency } mainly from use of distal ileum (**worst with Kock pouch – 80cm**)
- 5) Electrolyte abnormalities } depends on segment of bowel used
 } stomach → hypoCl, hypoK metabolic alkalosis
 } jejunum → hypoNa, hypoCl, hyperK metabolic acidosis
 } ileum and colon → hyperCl, hypoK metabolic acidosis
- 6) Renal failure } more common after ileal conduit cf colon conduits
- 7) Stones } most stones are **Ca/Mg/NH4/PO4**
 } more common w/ hyperCl met acidosis, pre-existing pyelo, & urease +ve UTI's
 } more common with ileal conduits (~10%) cf colon conduits (~4%)
 } even more common in colonic continent reservoirs (~20%)
→ worst with Kock pouch
- 9) Intestinal problems } malabsorption
 } diarrhea
 } loss of ileocecal valve
 } dehydration
 } short gut
- 10) Osteomalacia } **due to acidosis that reduces mineralized bone (release of Ca), renal Vit D resistance, or excessive Ca loss by kidneys**
 } most common with ureterosigmoidostomies
 } lethargy, joint pain (esp wt-bearing), proximal myopathy
Rx → correct acidosis, Ca +/- 1α-hydroxycholecalciferol supplements
- 11) Neoplasms } adenoCa, adenomatous polyps, sarcomas, TCC
 } usually don't manifest for 10-20yrs
 } **adenocarcinoma most common** and may develop from urothelium or bowel
 } most common when urothelium + colonic epithelium & both bathed by feces
Rx → routine C-scopes for ureterosigmoidostomies
→ annual surveillance of any diversion after ~3yrs
→ always remove ureterointestinal anastomoses after defunctionalized
- 12) Sensorium alterations } from **hypoMg, drug intoxication, or abN NH4 metabolism**
 → most likely NH4 related (esp in cirrhotics)
 } can result in ammoniagenic coma
 } most common in ureterosigmoidostomies
Rx → rectal tube/foley + neomycin + low protein + lactulose
→ arginine glutamate (50g in 1L D5W) if severe

What are the factors that contribute to altered solute reabsorption?

→ **metabolic complications are the result of altered solute reabsorption**

- segment of bowel used
- surface area of bowel
- amount of time bowel is exposed to urine
- concentration of solutes in urine
- renal function
- pH of fluid

Which electrolyte abnormalities are seen with each type of diversion?

1) stomach } hypoCl, hypoK metabolic ALKALOSIS

→ **loss of HCl**

- } usually only a problem with renal failure or severe dehydration
- } can get syndrome of severe met. alkalosis
 - N/V, lethargy, muscle weakness, respiratory distress, seizures, ventricular arrhythmias
- } worse if concomitant elevated serum gastrin levels (>120ng/L) + overdistension

Rx → H₂ blockers, PPIs

→ **arginine hydrochloride**

→ **removal of gastric segment**

2) jejunum } hypoNa, hypoCl, hyperK metabolic ACIDOSIS

→ **excessive loss of NaCl + reabsorption of K⁺ and H⁺**

- } loss of NaCl results in dehydration & **elevated aldosterone** (also from hyperK)
- } lethargy, N/V, dehydration, muscle weakness, fever
- } associated with elevated renin & angiotensin
- } more common with more proximal segments and worsened by TPN therapy

Rx → rehydrate with NaCl

→ **fix acidosis with NaHCO₃**

→ **lasix for K**

→ **long term therapy with NaCl tabs, thiazide diuretics long-term**

3) ileum/colon } hyperCl hypoK metabolic ACIDOSIS

→ **absorption of ammonium (NH₄) chloride**

- } fatigue, anorexia, lethargy, weakness, weight loss, polydipsia
- } more common in ureterosigmoidostomies
 - most need maintenance alkali therapy
- } **associated with K depletion & hypoCa**
 - more common with continent diversions & ureterosigmoidostomies
- } usually clinically insignificant (10% of ileal conduits)

Rx → po NaHCO₃ or K citrate for acidosis

→ **chlorpromazine or nicotinic acid to reduce acidosis & hyperCl**

- **high doses of chlorpromazine can lead to tardive dyskinesia**

- **can't use nicotinic acid w/ liver failure or PUD**

→ **need to treat hypoK along with severe metabolic acidosis**

Table 80-10 -- Syndromes of Electrolyte Disturbances in Patients in Whom Bowel Is Interposed in the Urinary Tract

Syndrome	Segment	Symptoms	Associated Abnormalities
Syndrome of severe metabolic alkalosis	Stomach	Lethargy, muscle weakness, respiratory insufficiency, seizures, ventricular arrhythmia	Elevated aldosterone, hypochloremia, hypokalemia
Syndrome of hyperkalemia, hypochloremia, metabolic acidosis	Jejunum	Lethargy, nausea, vomiting, dehydration, muscle weakness	Elevated renin, angiotensin
Syndrome of hyperchloremia, metabolic acidosis	Ileum, colon	Fatigue, anorexia, lethargy, weakness	Total-body potassium depletion, hypocalcemia

What are the 3 causes of hypoK often seen with urinary intestinal diversions?

→ **not seen with jejunal segments**

→ **more common with colon segments**

- 1) renal K wasting from renal damage
- 2) osmotic diuresis
- 3) GI loss from secretion (minor role)

Why can it be hard to assess renal function in patients with intestinal diversions?

- 1) bowel alters osmotic content of urine } can't test concentration ability
→ H₂O deprivation + osmolality ($\geq 600 \text{ mOsm/kg}$)
- 2) bowel makes urine more alkaline } can't test acidification ability
→ measuring urine pH (≤ 5.8)
- 3) bowel reabsorbs some urea & creat } serum urea & creat not always accurate reflection of renal fxn

What are the causes of stones in urinary diversions?

- 1) local
 - **chronic UTI's (urea-splitting bacteria)**
 - **mucus**
 - **FB's (staples, sutures, catheter)**
 - urinary stasis
- 2) systemic
 - dehydration (diarrhea)
 - acidosis
- 3) decreased urinary inhibitors
 - **hypocitraturia (from acidosis)**
 - hypomagnesemia
- 4) increased lithogenic metabolic defects
 - hypercalciuria
 - hyperoxaluria (fat malabsorption)
 - hypersulphaturia
 - low urine pH (uric acid stones)

What GI problems can arise with urinary intestinal diversions?

- 1) jejunum } fat malabsorption (Vit A,D,E,K deficiency)
 - } Ca malabsorption
 - } folic acid malabsorption
 - } Fe deficiency
- 2) ileum } fat malabsorption (Vit A,D,E,K deficiency)
 - } vit B12 deficiency (anemia)
 - } bile salt malabsorption (diarrhea)
- 3) colon } water (diarrhea)
- 4) stomach } intrinsic factor deficiency (Vit B12 anemia)

When should +ve cultures from urinary diversions be treated with ABx?

- 1) symptomatic infection
- 2) culture dominant for *Proteus* or *Pseudomonas* } higher risk of stones & renal deterioration

Neuromechanical problems

What are the NEUROMECHANICAL issues of urinary intestinal diversions?

- 1) volume-pressure issues } depends on configuration of bowel
 - greater volume change after detubularization
 - } detubularizing segment increases volume by ~50%
 - goal is to create spherical vessel
 - } volume capacity increases with time
 - ileal pouch increases ~7fold after 1yr
 - 2) motor activity } detubularizing segment interrupts coordinated peristalsis
 - only temporary as coordinated activity returns after ~3 months
 - long term effects unclear
- detubularization & reconfiguration of bowel usually increases volume but its long term effect on motor activity & wall tension is unclear**

Chapter #81 – Cutaneous Continent Urinary Diversions

GENERAL CONSIDERATIONS

Which patients are considered poor candidates for continent diversions?

- | | | |
|---|--|---|
| <ul style="list-style-type: none">- quadriplegics- MS- the very frail- mentally impaired | $\left. \begin{array}{l} \backslash \\ / \end{array} \right\}$ | <p>ability to do CIC
is essential</p> |
|---|--|---|

What is the required pre-op w/u specific to a continent urinary diversion?

- 1) renal function } creat <1.8-2.0 mg/dL (160-180 μ mol/L) or creat clearance >40-60mL/min
- 2) hepatic function } normal
- 3) C-scope if using colon
- 4) site for stoma (just in case)

What are the indications for post-op TPN after continent diversion surgery?

- 1) projected paralytic ileus >4-5days
- 2) nutritional depletion pre-op

What are the important issues to address post-op after urinary diversion?

- culture urine prior to stent removal at ~1week } may also start Abx on spec prior to removal
- ensure pouch is intact & no extravasation at ureteral anastomosis before stent removal
- continent diversions } routine urine cytology + long term cystoscopic surveillance
- ureterosigmoidostomy } routine C-scope

CONTINENT URINARY DIVERSION

What are the 2 main categories of non-orthotopic continent urinary diversions?

- 1) continent catheterizable diversions (requires CIC at intervals)
→ Kock pouch, Double T, Indiana, Mainz I, Penn, gastric, etc
- 2) ureterosigmoidostomy + variations of
→ eg rectal bladder, sigmoid hemi-Kock w/ proximal colonic intussusception, Mainz II, etc

What are the CONTRAINDICATIONS to “rectal bladder” urinary diversions?

- “RURAL Diversion”
- Renal insufficiency/renal failure
- Ureters (dilated)
- RADs (extensive)
- Anal sphincter incompetent
- Liver failure
- Diverticulitis and other colorectal diseases

Variations of Ureterosigmoidostomy

What are the different types of “rectal bladder” urinary diversions?

→ **mixed urine & feces with continence dependent on anal sphincter**

→ all have rectal tubes transiently post-op

1) folded rectosigmoid bladder

- ureters anastomosed into serosal troughs not into taenia (Ghoneim)
- larger sigmoid reservoir
- serous-lined tunnel/trough prevents reflux
- lower complication rate than direct taenial implantation

→ most get **HYPERCHLOREMIC HYPOKALEMIC METABOLIC ACIDOSIS**

→ needs standing HCO_3 replacement + chronic Abx + K supplementation

→ nightly urinary drainage necessary } may need rectal tube qHS

→ ureterocolonic strictures common (25-35%)

→ routine post-op C-Scopes to monitor for colon CA

2) augmented valved rectum

- similar to standard ureterosigmoidostomy except proximal intussusception of sigmoid colon confines urine to smaller surface area
- rectum also patched with ileum to improve urodynamic properties of rectal reservoir
- less electrolyte abnormalities

3) Hemi-Kock and T-Pouch with valved rectum

- hemi-Kock or T-pouch constructed using doubly folded, marsupialized ileum and a proximal continence mechanism to prevent pouch-ureteral reflux
- pouch is then anastomosed to rectum as a patch
- intussusception of sigmoid colon proximal to anastomosis prevents urine refluxing up proximal colon

→ imaging prior to removal of ureteric stents and rectal tube

→ can get **HYPERCHLOREMIC HYPOKALEMIC METABOLIC ACIDOSIS**

→ electrolyte abnormalities slightly less common } may still need standing K citrate

→ consider nightly rectal tube

→ slightly less risk of colon CA

→ best suited for younger exstrophy patient

4) Sigma-Rectum Pouch (Mainz II)

- similar to standard ureterosigmoidostomy but w/ partial reconfiguration of rectosigmoid jxn
- simple and creates a low-pressure rectosigmoid reservoir with increased capacity
- better continence rates

→ can get **HYPERCHLOREMIC HYPOKALEMIC METABOLIC ACIDOSIS**

→ usually still need standing K citrate or HCO_3

5) rectal bladder

- ureters reimplanted into rectal stump + terminal sigmoid colostomy

6) **ureterosigmoidostomy**

- ureters reimplanted directly into intact sigmoid

→ **only as last resort due to severe long term complications**

→ **hyperCl hypoK met acidosis, malignancy, pyelonephritis are common**

Where are the 2 favorite sites for stomal location?

- What are some basic peri-op issues surrounding continent catheterizable diversions?

- ### What are the 4 techniques used to create a dependable, catheterizable continence mechanism?

- What are some of the criticisms of appendiceal catheterizable stomas?

- What size catheter can be used with each type of catheterizable diversion?

- What is the initial capacity of urinary pouches?

- ileal pouch } ~150cc
- right colon pouch } >300cc

What is “pouchitis”?

- pain in the region of the pouch + increased pouch contractility
 - often presents w/ temporary failure of continence mechanism
 - sudden explosive incontinence not dribbling incontinence
- Rx → Abx for minimum 10days

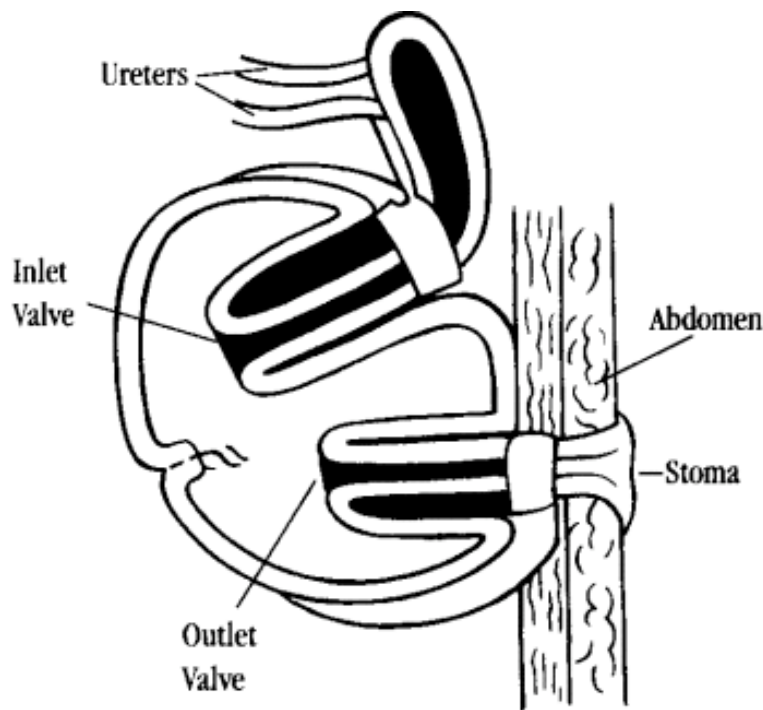
What is the management of intraperitoneal rupture of catheterizable pouches?

- more common in neurologic patients who have abN sensation
 - often associated with mild abdo trauma (eg fall)
 - requires immediate pouch decompression + imaging studies
- Rx → for large defects +/- peritonitis } surgical exploration + pouch repair is required
- Rx → for small defects + no peritonitis } catheter drainage + Abx may suffice
- } close monitoring essential

What is a Kock pouch?

→ **continence + anti-reflux + low-pressure reservoir**

- first described by Kock in '82 } since improved/modified by Skinner (USC)
 - **distal ileal pouch** + preservation of ileocecal valve } less diarrhea/steatorrhea
 - **uses 60-80cm of ileum**
- difficult & high complication rate } mostly abandoned but Kock limb still used
- highest rate of stones & Vit B12 deficiency

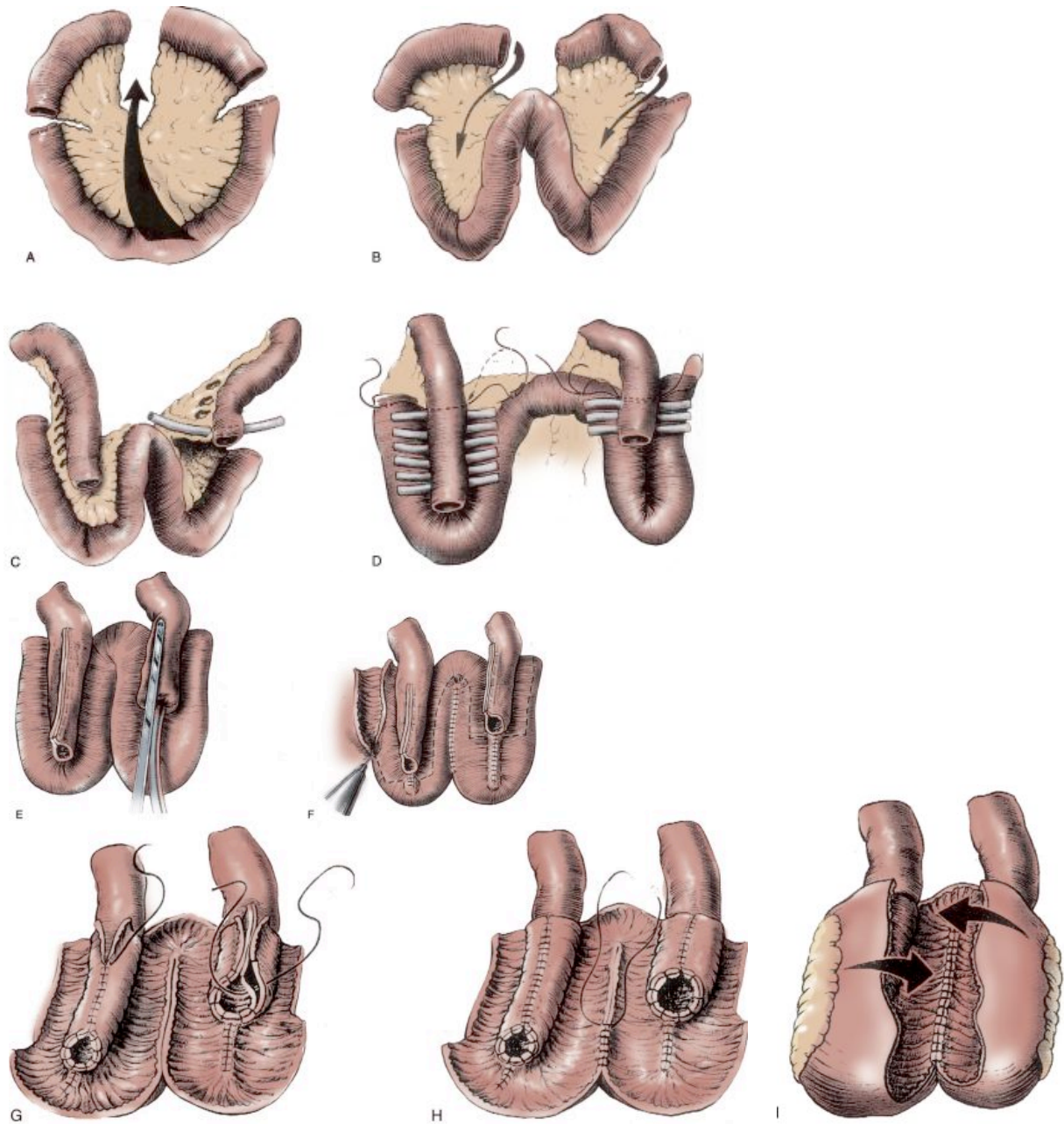


→ KOCK POUCH

What is a DOUBLE T POUCH?

→ **continent + antireflux + low-pressure reservoir**

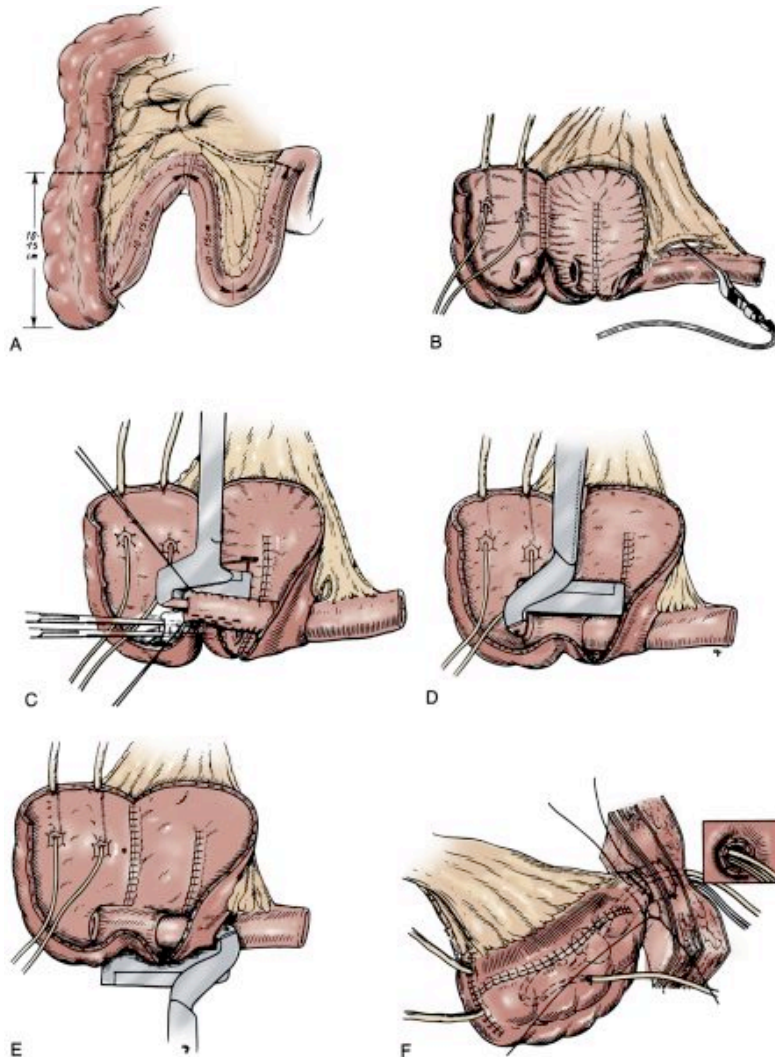
- Stein's (USC) modification of the original Ghoneim extramural serosal tunnel
- **requires ~70cm of distal ileum** (leave ~15cm of terminal ileum)
- preservation of ileocecal valve } less diarrhea/steatorrhea
- isoperistaltic anti-reflux limb (~11cm) & anti-peristaltic continence limb (~15cm)
 - both tapered with GIA
- middle segment (~44cm) folded in 'W' configuration
- large pouch capacity (~500cc)
- excellent long-term continence and anti-reflux



→ DOUBLE T POUCH

What is a catheterizable MAINZ POUCH I?

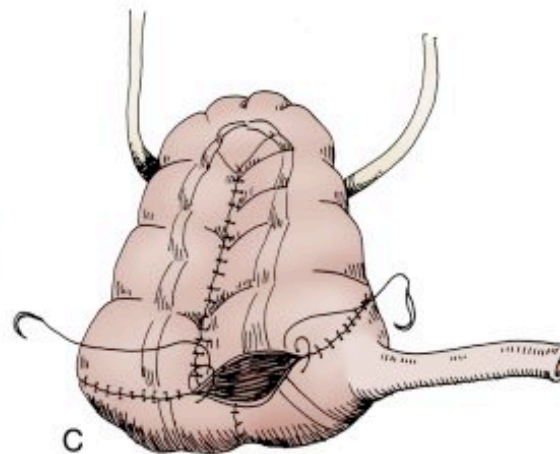
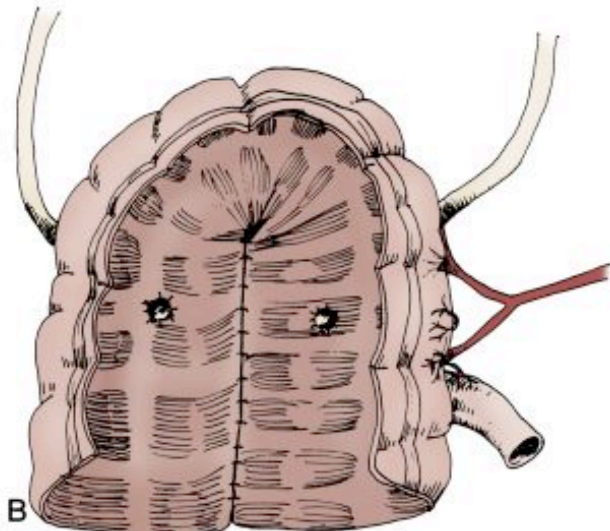
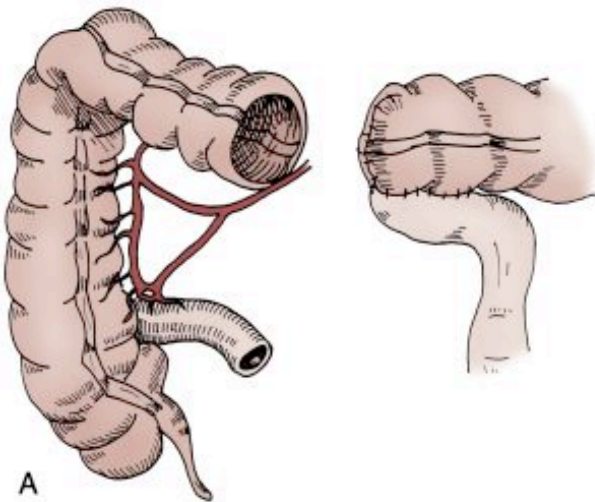
- **continent + fairly low-pressure reservoir** } +/- anti-reflux
- **10-15cm of cecum/ascending colon + 20cm of terminal ileum + 20cm of distal ileum**
- terminal ileum used as part of reservoir, distal ileal segment serves as catheterizable limb
- ureterocolonic anastomosis made at apex of reservoir
- distal ileal segment intussuscepted & placed through ileocecal valve then stapled in place
- largest pouch capacity (~600cc)
- different from orthotopic voiding Mainz pouch where ileocecal valve is used for anti-reflux
- better to **use appendix** instead of 20cm distal ileum } better continence rates & less complications
 - other options include } mitrofanoff-style tube of colon
 - } Yang-Monti-style conduit from 2-3cm distal ileum
 - } Woodhouse tapered tunneled ileum
- can use more ascending colon & less terminal ileum for pouch } less B12, bile salt, & fat absorption issues



→ MAINZ POUCH

What is an INDIANA POUCH?

- **continence + fairly low-pressure reservoir** } +/- anti-reflux
- first described by Rowland (Indiana U) in '87 } modified by Florida and U of Miami
- **10cm terminal ileum + entire ascending colon** to jxn of R & middle colic arteries (original)
- appendectomy
- tapered terminal ileum
- buttressed ileocecal valve } various techniques used
 - eg interrupted Lembert sutures over 12-14Fr catheter
- detubularization of entire colon and closed in Heineke-Mikulicz fashion
- uretero-taenial implants
- large capacity (~450cc)
- good continence rates
- easiest to make
- **very low complications**



→ INDIANA POUCH (Florida modification shown here)

What are the 3 types of R colon pouches with intussuscepted terminal ileum?

- 1) UCLA pouch
 - 2) Duke pouch
 - 3) Le Bag pouch
- all require appendectomy

What is a Penn pouch?

- **continence + fairly low-pressure reservoir } +/- anti-reflux**
- first continent diversion using Mitrofanoff principle
 - ileocecal pouch (Mainz pouch)
 - appendix removed with cuff of cecum
 - appendix reversed and a tunneled appendiceal-taenial implant is made
 - for additional length can make a tube of the base of the cecum
 - appendix may be used in situ as well (if long enough)
 - variations include a “reverse Indiana” } intact ileocecal valve for anti-reflux
 - also good for short ureters b/c terminal ileum can be left long to reach up high
 - } appendix for continence

What is a gastric pouch?

- **continent + fairly low**
- wedge-shaped segment of stomach off greater curvature (max width 7-10cm)
 - L gastroepiploic artery is used as blood supply } divide short gastrics near gastric fundus
 - if problem can use R gastroepiploic artery, dividing short gastrics to level of pylorus
 - one ureter tunneled into gastric reservoir
 - proximal TUU performed } ipsilateral distal ureter tunneled into reservoir and then used as catheterizable portal
 - can also make gastro-ileal pouch with implantation of ureters into gastric segment
 - 11cm segment of stomach isolated on R gastroepiploic artery
 - 22cm segment of ileum isolated and detubularized
 - Mitrofanoff continence mechanism used (tapered ileal segment)
 - low capacity reservoir
 - stomach mainly used for bladder augmentation NOT RESERVOIRS
 - may have role in paediatric population

What are the potential advantages of gastric pouches?

- less electrolyte reabsorption } better for patients w/ pre-existing metabolic acidosis or renal insufficiency
 - } NO hyperchloremic acidosis
- no issues with bowel shortening
- acidic urine may also decrease bacterial colonization
- good for patients with irradiated bowel
- minimal mucus production

QUALITY OF LIFE ASSESSMENTS

→ many studies have suggested an improved psychosocial adjustment of the patient undergoing continent urinary and fecal diversion compared with those patients with diversions requiring collecting appliances

→ NO RANDOMIZED PROSPECTIVE TRIALS COMPARING QOL AFTER CONTINENT CUTANEOUS DIVERSION WITH QOL AFTER NEOBLADDER OR CONDUITS

VARIATIONS IN OPERATIVE TECHNIQUE

What are the indications for converting a conduit to a continent reservoir?

→ **patient desire is only indication**

- use conduit when possible
- form of continent reservoir is an intra-op decision
- need full w/u prior to conversion
 - disease recurrence
 - renal function
 - urinary anatomy
 - hydronephrosis
 - intestinal length/health
 - hepatic function
- stomal stenosis & pouch stones are among the most common complications

What is the role of absorbable staples?

- eg. R colon pouch, Montie W-stapled ileal neobladder, stapled sigmoid reservoir
- substantially reduces time to make bowel reservoirs } detubularization essential to increase capacity and decrease peristalsis
- short-term & long-term reliability
- newer devices better b/c longer (cheaper) and not as wide (less bowel diameter sacrificed)
- essential not to overlap absorbable polyGIA staples because this will lead to failure of staples
- this changes technique for reservoir construction } bowel must be everted to reach deeper
- likely better for colonic pouches, which have larger lumens

Chapter #82 – Orthotopic Urinary Diversions

EVOLUTION OF URINARY DIVERSION

What are the 4 main classes of urinary diversions?

- 1) incontinent cutaneous conduits } eg ileal conduit
- 2) orthotopic diversions } eg Studer ileal neobladder, Mainz, T pouch
- 3) continent cutaneous diversions } eg Indiana pouch, Mainz I, Double T
- 4) continent rectal diversions } eg ureterosigmoidostomy, Mainz II, rectal bladder

What are the long term complications of ileal & colon conduits?

→ ileal conduit

- **pyelo (15-20%)**
- uretero-ileal strictures (~10%)
- stones (~5%)
- stomal stenosis (~10%)
- **renal deterioration (20%)**
- bowel obstruction (10%)
- hyperCl, hypoK, met. acidosis (13%)

→ colon conduit

- pyelo (10%)
- **uretero-colonic strictures (10-20%)**
- stones (~5%)
- stomal stenosis (~5%)
- renal deterioration (15%)
- bowel obstruction (5%)
- **hyperCl, hypoK, met acidosis (20-30%)**

Compare ileal conduits with colon conduits?

→ more common in ileal conduits

- pyelo
- stomal stenosis
- renal deterioration
- bowel obstruction

→ less common in ileal conduits

- hyperCl, hypoK, metabolic acidosis
- hypoK less severe
- uretero-enteric strictures (when non-refluxing colon conduit)

PRINCIPLES OF CONTINENT URINARY DIVERSION

List contraindications for continent orthotopic neobladder } “RUM RAIDS Liver”

→ ABSOLUTE }}} “RUM”

- Renal impairment (irreversible) } serum creatinine >2mg/dL (>180 µmol/L), creat clearance <60mL/min or proteinuria, inability to acidify urine, inability to concentrate urine

- Urethral TCC prior to cystectomy
- Margin +ve (intra-op distal urethral)

→ RELATIVE }}} “RAIDS Liver”

- RADs (extensive)
- Age or limited life expectancy (T3 or N+ disease should not be excluded automatically)
- IBD
- Dexterity issues (inability to do CIC, if necessary eg mental or physical impairments)
- Short bowel
- Liver failure

→ should be offered to all else

What are the 3 important principles of reservoir construction?

- 1) configuration } capacity increased by detubularizing bowel (sphere has largest capacity)
- 2) accommodation } relates to Laplace's Law
- 3) compliance } relates to type of bowel and the wall characteristics

Which segment of bowel is preferred for neobladder creation in patients with renal insufficiency?

→ gastric neobladder

- less solute reabsorption
- excretion of HCl means no hyperchloremic metabolic acidosis
- also have less mucus production & lower incidence of bacteriuria (acidic urine)
- excellent muscle backing for creation of anti-refluxing ureteral anastomosis
- also good for patients with short bowel syndrome

→ BUT ...

- can get hypoNa, hypoCl metabolic alkalosis
- risk of severe hematuria-dysuria syndrome & PUD (↑'d gastrin)
- poor urodynamic parameters } higher rate of incontinence & lower capacity

What makes ileum most suitable for reservoir construction?

- less contractility
- more compliance
- lower filling & capacity pressures
- superior urodynamic parameters
- ileum easy to manipulate surgically
- mucosal atrophy (decreased reabsorption) more reliably seen in ileum

SELECTION OF PATIENTS

What are the 2 important criteria that must be maintained in considering a patient for neobladder?

- 1) integrity of rhabdosphincter mechanism } essential for continence
- 2) cancer control shouldn't be compromised } frozen-section of urethral margin essential

CONTINENCE MECHANISM IN PATIENTS UNDERGOING ORTHOTOPIC DIVERSION

What is the innervation of the urethra?

- 1) pelvic plexus } autonomic nerves that serve the smooth muscle sphincter of BN
 } nerves run from pelvic plexus toward BN and very proximal urethra along lateral aspect of rectum (and vagina)
 → these nerves are taken during extirpative portion of OR
- 2) pudendal nerve } somatic nerves to EUS (rhabdosphincter)
 } perineal portion of pudendal nerve courses underneath UG diaphragm, deep to levators, and enters urethra laterally
 → **preservation of EUS & pudendal nerves are essential to continence**
 → to preserve continence, minimal dissection should be undertaken anteriorly along the pelvic floor

How does Radical Cystectomy affect urethral pressures?

- abolishes N reflex rise in urethral pressure with reservoir filling (no autonomics)
- no afferent input from detrusor } maintained after RP

CONTINENCE PRESERVATION

What are the main influences on continence after orthotopic neobladder?

- 1) reservoir characteristics (large capacity, low pressure)
 - 2) outlet integrity (EUS preservation)
- **N reflex rise in urethral pressure during bladder filling is lost after radical cystectomy**
- **explains worse incontinence at night**

What is the benefit of nerve-sparing radical cystectomy?

- not just saving somatics to EUS (pudendal nerves) but also the autonomic supply to corpora cavernosa and membranous urethra (pelvic nerve & inferior hypogastric plexus)
- improves day & night continence } greatest impact on daytime continence
- role in women is debatable
- may simply be a result of a more careful and meticulous dissection around the prostatic apex, with subsequent reduced damage to the EUS

How common is urinary incontinence for patients with neobladders?

- daytime } 10-15%
- nocturnal } 25-30%

What are the main clinical goals of a patient with a neobladder?

- 1) volitional voiding every 3-4hrs
- 2) capacity in the range of 400-500cc
- 3) low-pressure storage (<15cm H₂O)
- 4) nocturnal incontinence ≤25% (more common than daytime incontinence ~15%)

What are the RFs for daytime incontinence in patients with a neobladder?

- 1) advanced age of patient (>65yrs)
 - 2) use of colon segment (less compliant)
 - 3) lack of nerve-sparing technique (only in some series)
- improves early on with increasing neobladder capacity (may take 6-12 months)
- can worsen with age } decreased EUS function with age
- } loss of urethral sensitivity to urine + subsequent loss of reflex increase in tone

What is the management of persistent incontinence after orthotopic neobladder?

- persistent if present after 6-12 months } UDS to assess capacity & VLPP
- 1) mildly reduced VLPP } bulking agents (poor long-term results)
- 2) moderate/severe reduced VLPP } AUS in men & PVS in women (better long-term results)

How common is urinary retention in patients with a neobladder?

- 5-25% and usually more common in F
- likely a mechanical thing } pouch falls back in wide pelvic cavity, resulting in acute angulation of pouch-urethral junction
- } pouch may also herniate through prolapsed vaginal stump

What are the RFs for urinary retention in patients with a neobladder?

- 1) use of excessive intestinal length (>60cm of ileum)
 - 2) following nerve-sparing procedures
 - 3) increasing length of f/u
 - 4) incisional or abdo wall hernias
- Rx → repair of any hernias
→ CIC

What surgical techniques are important in optimizing urinary continence post-orthotopic neobladder?

- 1) minimal manipulation of:
 - a) muscle fibers of the EUS
 - b) fascial attachments
 - c) corresponding innervation (perineal branch of pudendal nerve)
- 2) in M, minimal dissection of pelvic floor & anterior urethra
 - minimize dissection of puboprostatic ligaments
- 3) in F, careful dissection of the posterior plane (between bladder and vagina) with vascular pedicle dissected sharply and carried down just distal to vesicourethral junction
 - use the Foley balloon to identify the vesicourethral junction
 - if the tumour is large, the anterior vaginal wall may be taken en bloc with the cystectomy specimen (NOT A CONTRAINDICATION to orthotopic neobladder)

What is the management of the vagina after radical cystectomy if vaginal-sparing surgery is the goal?

- 1) vagina closed at apex then suspended
 - suspend to Cooper's ligament
 - colposacroplexy with Marlex mesh
- 2) if vaginal vault reconstruction required may used:
 - rectus myocutaneous flap
 - detubularized cylinder of ileum
 - peritoneal flap
 - omental flap
- 3) well-vascularized omental pedicle graft must be placed between reconstructed vagina & neobladder
 - properly secure to levator ani muscles to separate suture lines and prevent fistulization between vagina and urethroenteric anastomosis or neobladder
 - omental pedicle will also prevent angulation of neobladder in capacious pelvic cavity (decreases risk of retention)

URETHRAL AND PELVIC RECURRENCE IN PATIENTS WITH BLADDER CANCER AFTER CYSTECTOMY

Urethral Recurrence

What are the sources of urethral TCC after radical cystectomy?

- 1) de novo TCC from "field change" of the urothelium } most cases
- 2) unrecognized TCC in the urethra at the time of cystectomy
- 3) growth of TCC from a +ve margin
- 4) recurrence from tumour spillage or implantation

How common is urethral recurrence AFTER RADICAL CYSTECTOMY?

- **more common after diversion than orthotopic neobladder (likely biased groups)**
- **in men** → **~10% urethral recurrence rate (usually within first 24 months)**
 - 5yr probability of urethral recurrence is 5% if no prostate involvement
 - ~15% 5yr recurrence rate if prostatic urethral or ductal involvement
 - highest rate of anterior urethral recurrence with prostatic stromal invasion (20-60%)
- **in women** → **2-12% have urethral involvement at time of cystectomy**
 - **1-2% recurrence rate**
 - presence of cancer at BN correlates with presence of urethral cancer

What are the RFs for development of urethral recurrence after cystectomy?

- 1) prostatic involvement (most ominous risk factor)
 - PROSTATIC STROMAL involvement is MOST PREDICTIVE RISK FACTOR
 - also higher risk if prostatic ductal involvement
 - no increased risk if only prostatic urethral mucosa involved
 - 2) cutaneous diversion
 - orthotopic neobladder decreases risk (5% vs 10%)
 - 3) BN involvement in WOMEN
 - 4) anterior vaginal wall involvement (pT4) in WOMEN
- *** **bladder CIS & multifocal tumours are NOT SIGNIFICANT RISK FACTORS** ***

How does urethral recurrence present?

- usually symptomatic } bloody urethral discharge, gross hematuria, or changes in voiding pattern
- +ve cytology in >90%

What is the recommended management of the retained urethra?

- 1) orthotopic neobladder
 - annual voided cytology
 - cystourethroscopy if urethral symptoms or changes in voiding pattern or continence
 - consider surveillance cysto of neobladder after 3yrs (Ca risk)
- 2) cutaneous diversion
 - delayed urethrectomy if +ve prostatic stromal involvement
 - cystourethroscopy if urethral symptoms or bloody discharge

What are the indications for urethrectomy?

- in men }
 - 1) ?CIS or gross tumour involving urethra (especially prostatic urethra or stroma)
 - 2) +ve distal urethral margin
 - 3) urethral recurrence post-cystectomy
- in women }
 - 1) ?CIS or gross tumour involving BN, urethra, or anterior vaginal wall
 - 2) +ve urethral margin
 - 3) urethral recurrence post-cystectomy
- required in <5% of patients
- RFs for urethral recurrence include }
 - prostatic stromal involvement in men
 - BN or anterior vaginal wall involvement in women
 - cutaneous diversion
- CIS & multifocality NOT risk factors for urethral involvement

How common is concomitant urethral TCC in women at the time of cystectomy?

- 50% if BN involvement \ 5-10% overall have
- 0% if BN is NOT involvement / urethral involvement

Pelvic Recurrence

How common is local pelvic recurrence after radical cystectomy?

- ~10% overall } ~5% if organ-confined + LN -ve
- } ~15% if not organ-confined (LN status doesn't matter)

What is the role for orthotopic neobladders in locally advanced or LN +ve bladder cancer?

- local recurrence not very common (~15%)
 - can live decent length of time (60% 10yr survival for T3 and 33% 10yr survival for LN+ve)
 - local recurrence rarely affects neobladder function
 - patients with local recurrence usually die of systemic disease not consequences of neobladder
 - type of diversion doesn't change risk of complications, ability to receive salvage treatment or overall survival once pelvic recurrence is diagnosed
- should NOT BE A CONTRAINDICATION

PREVIOUS PELVIC RADIATION

What are some of the concerns regarding salvage cystectomy post-pelvic RADs?

- radiation-induced vasculitis
- fibrosis of ureters and bowel
- local ischemia affecting tissue healing

What is the role for orthotopic neobladder after salvage cystectomy post-pelvic RADs?

- safe in select patients post-radical RADs for bladder Ca, prostate Ca, gyne Ca
- higher incontinence rates } **~25% require AUS or sling**

ORTHOTOPIC DIVERSION AND THE NEED TO PREVENT REFLUX

What are the arguments FOR & AGAINST the need for anti-reflux mechanisms in neobladders?

FOR	AGAINST
<ul style="list-style-type: none">- normal human bladder is non-refluxing- some evidence suggests decreased renal deterioration if reflux prevented (less bacteria & urine solutes)- anti-reflux in chronically infected continent cutaneous reservoirs is not a source of debate and many patients w/ neobladders will need CIC, leading to chronically infected urinary reservoirs- newer anti-reflux mechanisms have fewer complications- ~40% with neobladders will ultimately need to perform CIC- need extra 20cm of ileum (total 60cm) to make Studer afferent limb	<ul style="list-style-type: none">- neobladders are large volume, low-pressure reservoirs- urine should be sterile in neobladder- the Valsalva used to empty a neobladder is also transmitted to the upper tract preventing reflux- technically too demanding- complications (ie ureteric strictures) are more common, outweighing benefits of anti-reflux- harmful effects of urinary constituents from reflux only shown in animals- isoperistaltic long afferent limb of Studer ileal neobladder has good results and negates need for anti-reflux- upper tract deterioration usually takes >15yrs

What are the 3 most common complications related to the intussuscepted nipple valve?

➔ **overall complication rate of ~10%**

- stone formation (5%)
- afferent nipple stenosis (4%)
- prolapse of afferent limb (1%)

What are the advantages of the Ghoneim extramural serous-lined ileal neobladder (anti-reflux)?

➔ **continent + anti-reflux + low-pressure reservoir**

➔ modified by Stein et al for continent cutaneous diversions (double-T pouch)

- 1) only 40cm of ileum required for entire reservoir } less metabolic complications
- 2) no metallic staples required } less stones
- 3) low incidence of ureteral anastomotic strictures
- 4) even grossly dilated ureters not a contraindication
- 5) not technically difficult

TECHNIQUES OF ORTHOTOPIC BLADDER SUBSTITUTES

Describe the different types of orthotopic neobladders?

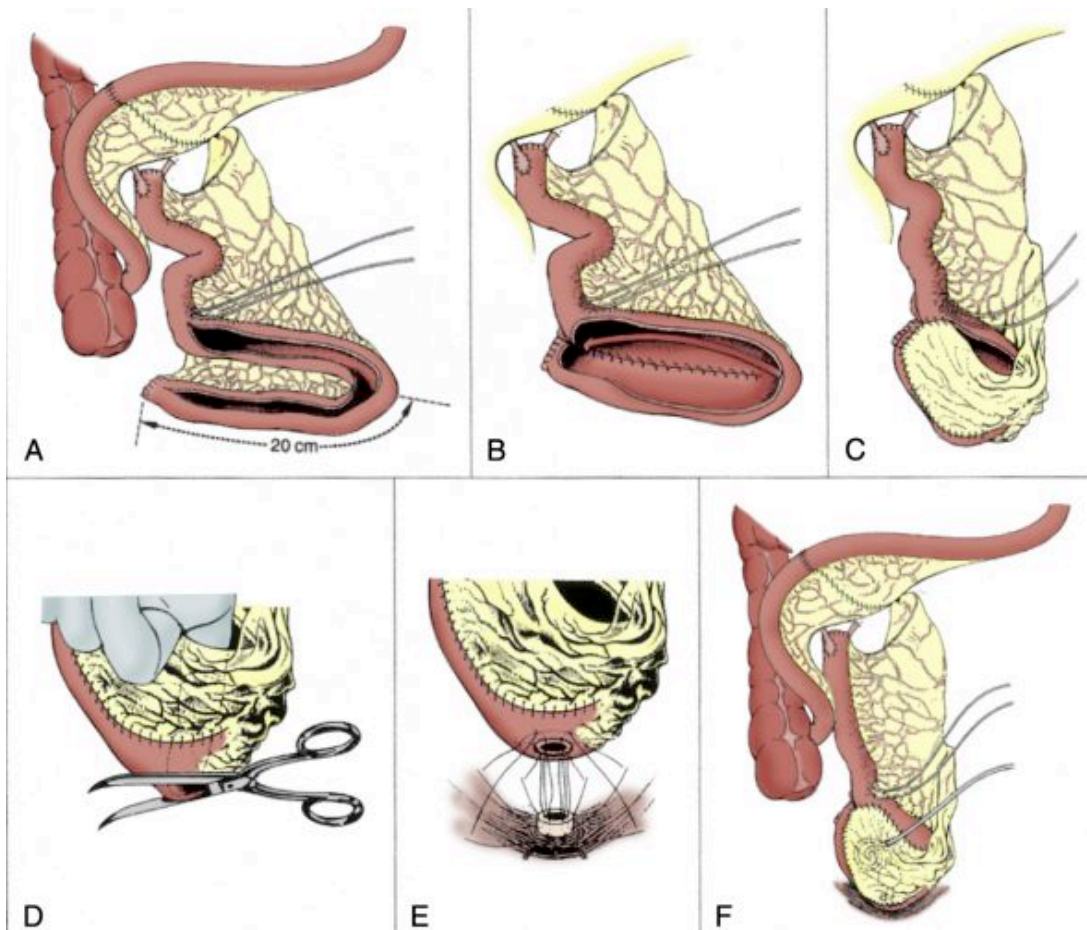
A) REFLUXING

- 1) **Studer ileal neobladder (one of the most popular neobladders)**
 - **long, afferent, isoperistaltic limb**
 - ~**60cm of ileum** required (starting 25cm proximal to IC valve)
 - detubularization of only the distal 40cm of ileal segment
 - proximal 14-20cm forms an isoperistaltic afferent limb
 - pouch made in U configuration to form a sphere
 - ureters implanted in **refluxing Bricker fashion**
 - buttonhole in most dependent part of pouch anastomosed to urethra
- 2) **Le Bag ileocolic Pouch**
 - 20cm of terminal ileum + 20cm ascending colon required
 - detubularization of entire ileum and colon and pouch formed in U configuration
 - ureters anastomosed to colon in **refluxing Bricker fashion along teniae**
 - proximal end of ileum anastomosed to urethra } neobladder is in inverted position
(cecum pointing cephalad)

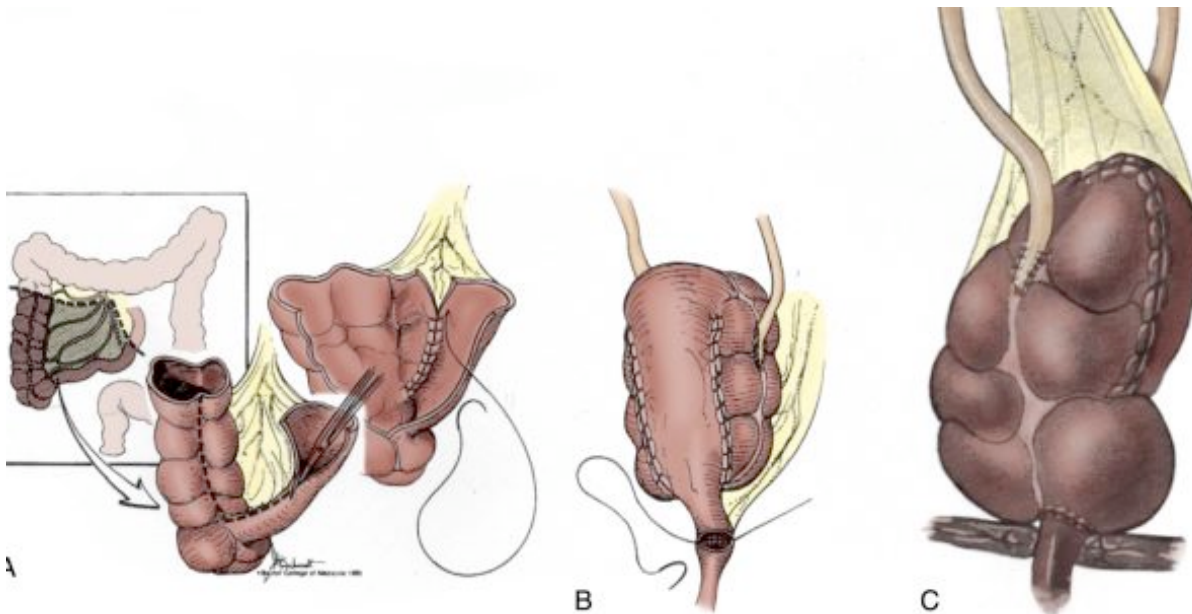
B) ANTI-REFLUX

- 1) **Mainz Pouch**
 - **initially for continent cutaneous reservoir**
 - **mixed ileum and cecum pouch**
 - 20-30cm of ileum + 10-15cm of cecum/ascending colon required
 - detubularization of entire ileum and colon and pouch formed in W configuration
 - ureters anastomosed to distal end of colon in **anti-reflux Goodwin fashion**
 - buttonhole at base of cecum is anastomosed to urethra
- 2) **T Pouch Ileal Neobladder**
 - **Kock pouch + serous-lined ileal trough instead of intussuscepted nipple valve**
 - **less ileum required**
 - **no nipple valve so less complications & no staples so less stones**
 - **anti-reflux trough preserves blood supply so less ischemic stenosis of valve**
 - **can overcome short ureters by harvesting longer afferent ileal limb**
 - 44cm of ileum required for pouch and afferent ileal limb is ~ 8-10cm } total 52-54cm
 - detubularization of entire 44cm segment and pouch formed in V configuration
 - afferent ileal limb placed in serous-lined trough and distal 3-4cm are anchored
 - ureters anastomosed to non-refluxing afferent ileal limb in **Bricker fashion**
 - buttonhole in most dependent portion of pouch is anastomosed to urethra
- 3) **Hautmann ileal neobladder**
 - **modification uses less ileum (40cm) & ureters implanted in refluxing fashion**
 - **large capacity neobladder to reduce nocturnal incontinence**
 - 70cm of terminal ileum required
 - detubularization of entire ileal segment leaving small flap for urethral anastomosis
 - pouch made in W configuration
 - ureters implanted in **non-refluxing Le Duc fashion**
 - urethral anastomosis made via buttonhole made in previously created flap
- 4) **Serous-lined, extramural ileal neobladder (Ghoneim)**
 - **no staples or synthetic material, short segment of bowel req'd, ureter heals easily**
 - 40cm of ileum required
 - detubularization of entire segment and pouch made in W configuration
 - serous-lined intestinal troughs made and **ureters laid down in troughs for anti-reflux**
 - mucosal edges reapproximated over implanted ureters
 - buttonhole placed in most dependent portion of pouch and anastomosed to urethra

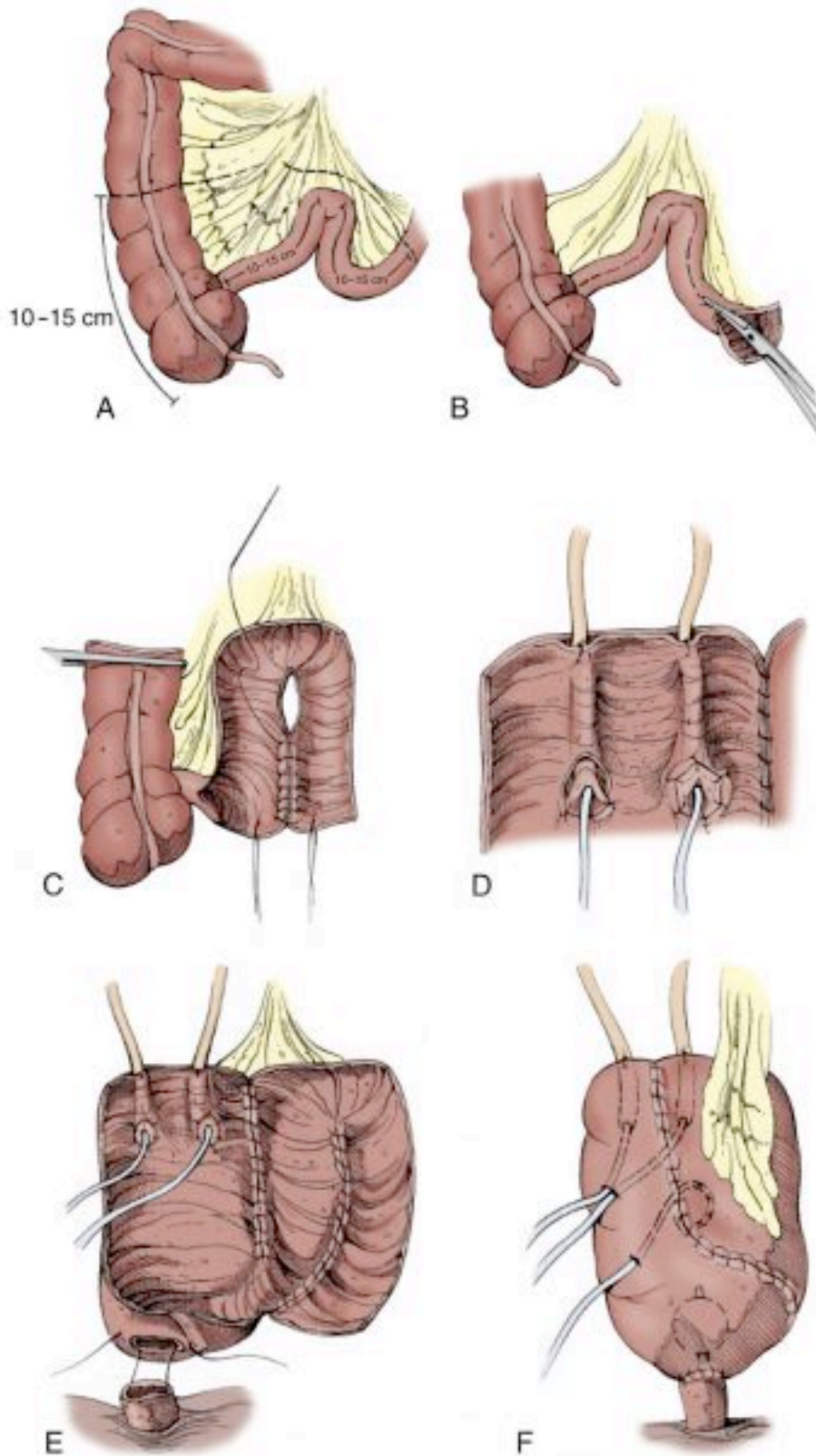
- 5) Kock ileal neobladder
- **initially for continent cutaneous reservoir (2 intussuscepted nipple valves for anti-reflux and continence)**
 - ~60cm of ileum required
 - proximal ~20cm used to form **anti-reflux intussuscepted nipple valve**
 - ureters anastomosed to non-refluxing proximal limb in **Bricker fashion**
 - distal ~40cm detubularized and used to form pouch in U configuration
 - most dependent portion of pouch becomes neourethra
 - **difficulty of intussuscepted nipple valve + associated complications have made this a less favorable option**
- 6) Right Colon Pouch
- entire cecum + ascending colon required
 - ileal stump of IC valve closed off and appendix removed
 - detubularization of colon (along anterior taenia) except proximal 5-8cm of cecum
 - colon pouch made in Heineke-Mikulicz fashion (vertical incision closed horizontally)
 - ureters anastomosed to colon in **anti-reflux Goodwin fashion**
 - buttonhole in base of cecum anastomosed to urethra
- 7) Camey II
- ~65cm of ileum required
 - detubularization of entire segment and pouch formed in U configuration
 - ureteroileal anastomosis made in anti-reflux **Le Duc fashion**
 - urethral anastomosis made in preselected area of pouch
 - modifications exist eg Z shape pouch or VIP pouch (Padua, Italy)
- 8) S bladder (Schreiter and Noll)
- ~75cm of ileum required
 - detubularization of ileum except distal 5cm and proximal 15cm
 - detubularized central portion of ileum used to form pouch in S configuration
 - proximal 15cm used to form **anti-reflux Kock nipple**
 - ureters attached to this limb in refluxing Bricker fashion
 - distal 5cm taped down to size of urethra and anastomosed
- 9) Reddy Sigmoid Pouch
- **neobladder with least amount of bowel used**
 - 35cm of descending colon and sigmoid required
 - pouch made in U configuration
 - detubularization of colon segment except at base (knuckle) of U
 - ureters anastomosed to colon in **anti-reflux Goodwin fashion** } **one ureter per limb**
 - buttonhole at base of U pouch anastomosed to urethra



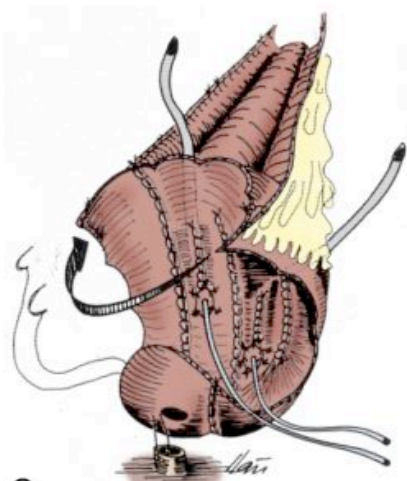
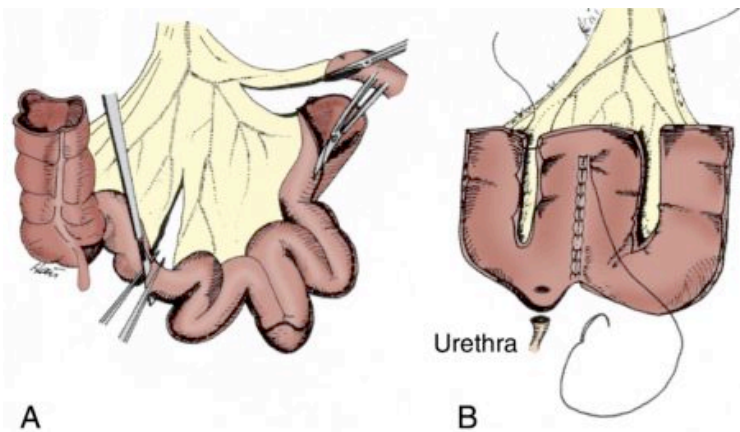
→ **STUDER ILEAL NEOBLADDER (refluxing)** } ~60cm total (25cm from IC valve)



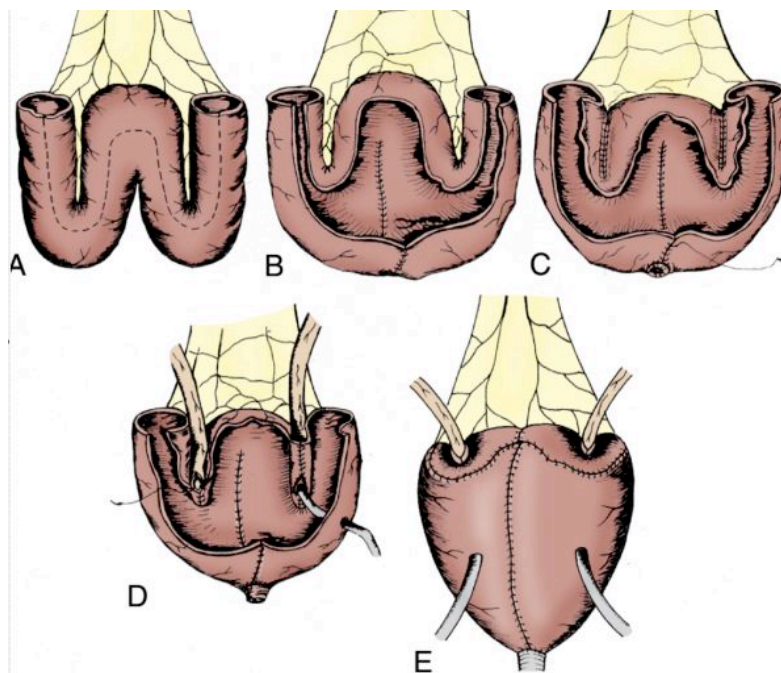
→ **LE BAG POUCH (refluxing)** } 20cm of ascending colon + 20cm terminal ileum



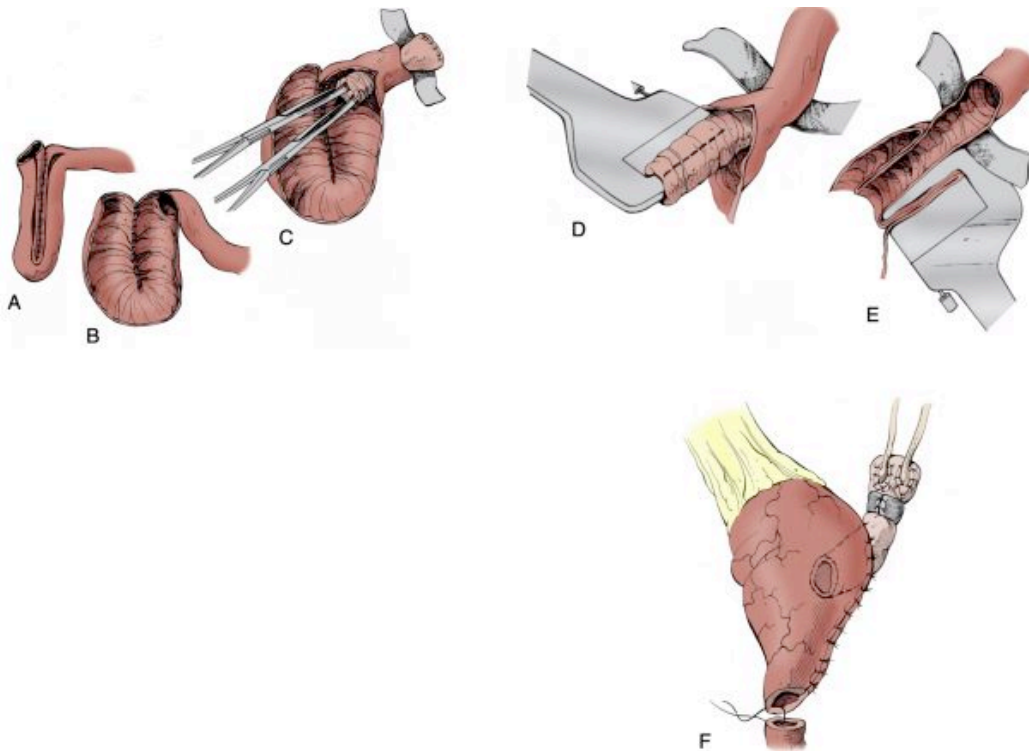
→ MAINZ ORTHOTOPIC NEOBLADDER (anti-reflux) } 20-30cm terminal ileum + 10-15cm colon
 } Goodwin reimplantation (anti-reflux)



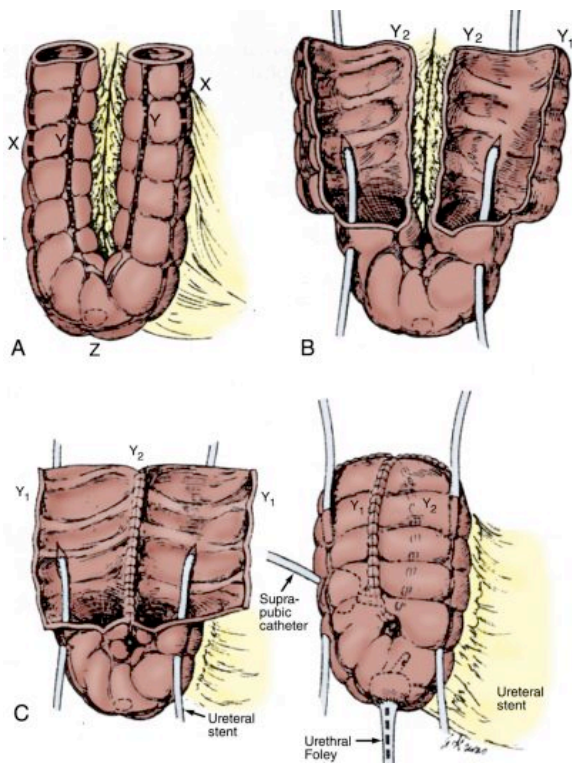
→ HAUTMANN ILEAL NEOBLADDER (anti-reflux) } ~70cm ileum + Le Duc reimplant



→ GHONEIM SEROUS-LINED EXTRAMURAL ILEAL NEOBLADDER (anti-reflux) } 40cm



→ KOCK ILEAL NEOBLADDER (anti-reflux) } 60cm total (20cm intussuscepted nipple valve)



→ REDDY SIGMOID POUCH (anti-reflux) } 35cm colon total
 } Goodwin reimplantation (anti-reflux)

What drains/catheters are recommended after creation of a neobladder?

- ureteral stents } can be externalized or internalized and anchored to urethral catheter
 } for 1-2 weeks
- urethral catheter ($\geq 24\text{Fr}$) } for $\sim 3\text{wks}$
- pelvic drain } JP or Penrose that is removed after urethral catheter is removed
- cystostomy tube } not recommended by all
- gastrostomy tube } not recommended by all

What is the management of a urine leak in a patient with a neobladder?

→ routine imaging of the neobladder debatable

- 1) conservative management } pull pelvic drain out slightly and maintain urethral drainage
- 2) proximal diversion with bilateral NTs
- 3) open surgical drainage } ONLY if persistent leak with FB present or if an undrained fluid collection can't be managed with CT-guided drainage
 } frank dehiscence and/or peritonitis is also an indication

RESULTS OF ORTHOTOPIC SUBSTITUTES

What are the arguments for an orthotopic neobladder being the gold standard (and not an ileal conduit)?

- superior cosmetic result
- more natural voiding
 - 80-90% continence
- no significance difference in peri-op mortality & complication rate
 - both have mortality rate ~2-3% and complication rate ~30%
 - 5-15% early complications
 - 10-25% late complications

What are some complications specific to, or more common in, orthotopic neobladders?

- 1) incisional hernias } from Valsalva
 } 50% require re-OR
- 2) neobladder-cutaneous fistulae
- 3) neobladder-vaginal fistulae
- 4) urine leak } most managed conservatively

USE OF ABSORBABLE STAPLING TECHNIQUES IN ORTHOTOPIC SUBSTITUTES

What is the role of absorbable staples in orthotopic neobladders?

- decreases the time of detubularization and refashioning of the bowel, which is necessary to create a large-capacity, low pressure reservoir with elimination of coordinated peristaltic bowel activity
- initially role was limited due to the bulky nature of the staples
- newer staples are longer and less bulky
- long term results will delineate appropriate application

QOL AFTER URINARY DIVERSION

What are the potential QOL disadvantages of an orthotopic neobladder?

- 1) post-operatively, patients are left with indwelling catheters and drains longer
- 2) requires vigilance and effort to maintain neobladder properly
- 3) may require CIC and irrigation of mucous
- 4) may have slightly higher risk of bowel dysfunction (diarrhea & Vit B12 malabsorption) due to increased bowel length required for most neobladders
 - ileal conduit is only ~15cm
 - least amount of bowel used is 35cm in Reddy Sigmoid pouch or 40cm in Ghoneim ileal neobladder

How is the QOL after orthotopic neobladders?

- current literature can't conclude that any form of urinary diversion is superior to another on the basis of health-related QOL outcomes
- most QOL studies that compared various types of urinary diversions have been criticized for methodological problems that limit their conclusions

Chapter #83 – Genital and Lower Urinary Tract Trauma

INJURIES OF THE EXTERNAL GENITALIA

Penis

What is a penile fracture?

- **tear in tunica albuginea** } bilaminar structure (inner circular & outer longitudinal)
→ outer is strength layer
- majority in N America from sexual intercourse (“faux pas du coit”)
- tunical tear is usually transverse & unilateral
- rupture can occur anywhere, but most are distal to suspensory ligament
- **rupture of dorsal penile artery or vein during intercourse may mimic penile #**

How is a penile fracture diagnosed?

- 1) history } sudden detumescence after pop or crack is heard
} pain and discoloration follow, with swelling of penile shaft
} eggplant deformity seen when Buck’s fascia remains intact
- 2) P/E } swollen, ecchymotic penis (often deviates away from side of rupture)
} swelling, bruising may extend to scrotum, perineum, S/P region if Buck’s fascia not intact
} tunical tear not always palpable
- 3) imaging } not usually necessary
} cavernosography is very time-consuming and hard to interpret
} U/S is easy and cheap but has high false negative rate
} MRI is very accurate in showing tunical rupture but labour intensive
→ if equivocal, MRI would be first line evaluation

How common is a urethral injury seen with penile fracture?

- more common in US and Europe (20%) VS Asia and Middle East (3%)
→ usually self-inflicted in Middle East (taghaandan)
- usually associated with gross hematuria, blood at meatus, or inability to void
- **LOW THRESHOLD FOR URETHROGRAPHY**

What is the management of penile fracture?

- 1) **early exploration & surgical repair has been shown to be of most benefit**
 - distal circumcising incision and degloving of penis
 - closure of tunical defect with interrupted 2-0 or 3-0 absorbable suture
 - avoid deep corporal vascular ligation and excessive debridement of delicate erectile tissue
 - concomitant urethral injuries should be repaired
→ oversew partial injuries over catheter
→ debride, mobilize, and repair complete injuries over catheter
- 2) Abx
- 3) 1 month abstinence

What are the benefits of early surgical repair of a fractured penis?

- faster recovery
- decreased morbidity (abscesses, debilitating plaques, ED, etc)
- lower complication rates
- lower incidence of long-term chordee

How do GSWs to the penis present?

- **80% have other associated injuries**
 - abdominal, pelvis, lower extremity, vascular, inguinal, other GU
- **good cosmetic & functional outcomes with early exploration & reconstruction**
- 15-50% have urethral injuries
 - strongly consider RUG for patients w/ penetrating injury to penis (blood at meatus, difficulty voiding, close to urethra, etc)
 - repair of all urethral injuries should follow standard urethroplasty principles
 - if injury is extensive, often need staged repair + urinary diversion

What are the management principles for GSWs to the external genitalia?

- immediate exploration
- copious irrigation
- excision of foreign matter
- Abx prophylaxis
- surgical closure

What is the management of bites to the penis?

- dog bites most common } copious irrigation + debridement
 - } immediate primary closure
 - } prophylactic ABx
 - Keflex + PenV (500mg qid) for *Pasteurella multocida*
 - } tetanus + rabies immunization
- human bites } usually present later than animal bites, so often infected
 - } similar Rx as animal bites but need to cover *Eikenella corrodens*
 - **DO NOT CLOSE HUMAN BITES PRIMARILY**

What is the management of penile amputation?

- **if acute presentation, microvascular replantation is treatment of choice**
 - if no micro surgeon available, transfer to another institution
 - clean and wrap amputated portion in sterile NS-soaked gauze then put in sterile bag
 - **can re-implant up to ~18hrs**
 - 2 layer spatulated urethral anastomosis over catheter
 - **microvascular repair of dorsal artery, vein & nerves preferred**
 - repair tunica albuginea with interrupted sutures
 - coverage with native skin
 - S/P tube
 - if microvascular surgeon unavailable, replantation using McRoberts principles +/- leeches
- if amputated portion is unavailable,
 - close corporal bodies with 4-0 PDS
 - spatulate urethral meatus to tunica
 - cover penile shaft (+/- STSG) } can also bury shaft under skin of scrotum
 - delayed phallic reconstruction or penile reconstruction
- consider psych consult if self-inflicted (most cases -65-90%)

What are the key steps to penile replantation?

- wrap amputated penis in sterile gauze soaked in NS
- 2 layer urethral closure over catheter with 5-0 absorbable suture
- minimal dissection along neurovascular bundle to identify severed vessels and nerves
- closure of tunica albuginea with 3-0 absorbable suture
- microscopic anastomosis of dorsal artery with 11-0 nylon
- microscopic repair of dorsal vein with 9-0 nylon
- microscopic epineural repair of dorsal nerve with 10-0 nylon
- S/P cystostomy

How successful is penile replantation after traumatic amputation?

- 50% able to achieve erections
- sensation present in 80% after microscopic replantation

What are the complications of penile replantation?

→ less common with microvascular repair

- urethral strictures
- skin loss
- sensory abnormalities
- ED
- loss of appendage
- infection
- chordee

What is the management of zipper injuries of the penis?

- penile block
- lubricate sliding piece and adjacent skin with mineral oil
- one attempt to unzip
- cut cloth material between each tooth to release device
- bone cutter can be used to cut slide piece to allow zipper to fall apart
- some kids may need Cx or an elliptical skin excision under GA

What is the management of strangulation injuries of the penis?

- decompress constricted penis to allow blood flow and urination
- lubrication, bolt cutters, drills, etc may be needed

Testis

What factors protect the testis from injury?

- scrotal mobility
- reflex cremasteric muscle contraction
- tough fibrous tunica albuginea

What are the causes of testis trauma?

- 75% blunt trauma } assault, sports-related events, MVA
 } 1-2% are bilateral
- 25% penetrating trauma } GSWs, explosions, impalement injuries
 } 30% are bilateral
 } ~80% assoc'd w/ non-GU injuries (thigh, perineum, femoral vessels, etc)

How is testicular trauma diagnosed?

- physical exam } swelling & ecchymosis are variable
 - } degree of hematoma does not correlate with severity of testis injury
 - } absence of hematoma does not rule out testis rupture
 - } **r/o concomitant urethral injury**
 - } nonpalpable testis may represent a dislocated testis (outside of scrotum)
- imaging } U/S to assess integrity and vascularity of testis
 - inhomogeneity of parenchyma + disruption of tunica albuginea suggest testis fracture
 - 80% of significant hematoceles are due to rupture, regardless of imaging
 - } **if U/S is equivocal but physical exam is suspicious, always explore**

What is the DDx of testis fracture?

- hematocele without rupture
- testicular torsion
- reactive hydrocele
- hematoma of epididymis or spermatic cord
- intratesticular hematoma

What is the management of testicular trauma?

- **early exploration & repair is beneficial**
 - increased testis salvage
 - reduced convalescence time and disability
 - earlier return to normal activities
 - preservation of fertility and hormonal function
- goals include:
 - testis salvage
 - prevention of infection
 - control of bleeding
 - reduced convalescence
- scrotal incision preferred
- close tunica albuginea w/ absorbable sutures after removal of necrotic & extruded seminiferous tubules
- explore and drain intratesticular hematomas even in absence of testis rupture to prevent pressure necrosis and atrophy, delayed exploration, and orchiectomy
- close tunica albuginea ... leave tunica vaginalis open ... consider drain

What is the management of penetrating scrotal injuries?

- explore to r/o vascular and vasal injury
- vas injured in 7-9% of scrotal GSWs
- ligate injured vas with nonabsorbable suture + delayed reconstruction prn
- ~30% of GSWs injure both testes

What are the outcomes of testis rupture management?

- non-operative management often complicated by:
 - infection
 - atrophy
 - necrosis
 - delayed orchiectomy } 3-9fold higher (20-50%)
- **90% testis salvage rate with exploration + repair within 3 days of injury**
 - **33% salvage rate with conservative management**
- salvage rate for penetrating testis trauma is only 30-60%

Genital skin

What are the causes of genital skin loss?

- 1) **Fournier's gangrene } most common cause of extensive genital skin loss**
- 2) traction by mechanical devices (farm or industrial machinery)
- 3) suction devices (vacuums)
- 4) burns } usually full thickness because skin so thin

What are the signs, symptoms, and findings suggestive of Fournier's gangrene?

- significant genital edema and erythema
- skin ischemia (necrotic areas)
- subcutaneous air on U/S or CT
- pt usually unstable

What are the RFs for Fournier's gangrene? } } DAMPPP SCROOTI

- **DM**
- **Surgery** in local area
- **Alcohol** abuse
- **CIC** (urine extravasation)
- **Malnutrition**
- **Roids**
- **Perianal** disease
- **Old** age
- **Paraphimosis**
- **Obesity**
- **PVD**
- **Trauma**
- **Immunosuppression** (eg HIV)

What is the management of Fournier's gangrene?

→ **clinical suspicion & recognition is the key**

- systemic Abx, IVFs
- multiple debridements
- wet-to-dry dressings for skin loss
- S/P urinary drainage for extensive infections to simplify wound care and prevent urethral complications from prolonged catheterization
- may consider hyperbaric O₂
- thigh pouch or wet dressings for testes
- plastics consult for coverage



→ FOURNIER'S GANGRENE } edema, erythema, and central necrosis

What are the options for penile skin loss?

→ debride all avulsed skin

1) small defects

→ wet gauze dressing

→ use of excess foreskin (if unCx'd) may allow 1° closure of mid to distal skin loss

→ scrotal rotation flaps for more proximal defects } poor cosmesis due to hair

→ local flaps (abdomen, thigh) } cosmetically inferior to STSGs

2) larger defects

→ **thick, UNMESHED, STSGs preferred for extensive penile reconstruction**

- meshed grafts have better take but tend to contract and are less cosmetic

→ meshed ok if ED

- remove all subcoronal skin remaining after debridement (prevent lymphedema)

- skin grafts on penile shaft NEVER regain normal sensation

What are the options for genital burns?

→ ability to reconstruct damage depends on how well N structures have been maintained after the acute injury

→ **careful debridement is the rule in acute management (less aggressive due to unique vascularity of genital tissue)**

- urethral injuries often devastating } may need PU

- penis often incarcerated in contracted scar tissue } gracilis musculocutaneous flap to release shaft then STSG to cover it

- reconstruction often requires a number of stages

- early resection of burn eschar

- **early coverage with STSG when possible } silver sulfadiazine cream if only minor**

What are the options for scrotal skin loss?

- **scrotal skin defects $\leq 50\%$ can be closed primarily**
- for extensive defects, testes placed in thigh pouches or wet dressings until reconstruction
- **local skin flaps used to cover as much of defect as possible } medial thigh, rectus, etc**
- **MESHED STSGs used to cover rest of defect } improved take**
- neoscrotum may appear tight at first but does expand

What is the management of the STSG donor site?

- control bleeding by epinephrine-soaked Telfa dressing
- 1% silver sulfadiazine cream, Jelonet, 3% bismuth gauze
- place large semi-occlusive dressing
 - don't use vapour-occlusive dressings } high rate of infections
- remove dressings when lifts off spontaneously or if infection occurs

BLADDER INJURIES

What are the causes of bladder injury?

- **10-30% have concomitant urethral injuries**
- 1) blunt trauma } mostly from rapid deceleration MVCs, falls, crush injuries, etc
 - } rarely isolated injuries (80-95% have non-GU injuries)
 - } **pelvic fracture associated with ~90% of bladder injuries**
 - **only 5-10% of pelvic fractures have bladder injuries**
- 2) penetrating trauma } GSWs and stabbings
- 3) iatrogenic injury } Obs/Gyne complications are the most common
- 4) spontaneous } altered sensorium

What are the signs, symptoms, findings suggestive of bladder injuries?

- **gross hematuria or clots in urine } present in >90%**
- S/P tenderness or pain
- lower abdo bruising or signs of perineal or genital trauma
- abdo distension or ileus or decreased bowel sounds
- inability to void or low u/o
- free intraperitoneal fluid on CT or ultrasound
- pre-existing bladder disease or urologic surgery
- unresponsive, intoxicated, or altered sensorium

What are the indications for cystography?

- **ABSOLUTE**
 - gross hematuria + pelvic fracture } 30% have bladder rupture
- **RELATIVE**
 - gross hematuria + blunt trauma
 - microhematuria + pelvic fracture
 - high index of suspicion for bladder injury
 - penetrating trauma of pelvis/lower abdomen + any degree of hematuria
 - hx of prior bladder augmentation

How do you perform a proper cystogram?

- fill until patient feels discomfort or until 350mL
 - 30% contrast (no dilution)
 - fill by gravity
- 3 views taken } pre-fill film, full bladder AP, and drainage films

What are the findings on cystogram that suggest bladder injury?

- extraperitoneal } flame-shaped collection of contrast in pelvis
 } amount of extravasation not always proportional to extent of injury
 } may extend up retroperitoneum or down into scrotum or perineum
- intraperitoneal } contrast outlines loops of bowel
 → avg size of injury is 6cm

What is the role of CT cystograms?

- CT routinely done for trauma } has replaced plain film cystograms
- bladder must be filled retrogradely to a volume of 350-400mL
 → **dilute 30% down 6:1 in NS to get ~4% contrast solution**
 → **antegrade filling of bladder after clamping is NOT ADEQUATE**
- no drainage films needed
 → posterior injuries can be seen

How do you classify bladder injuries?

- 1) contusions
- 2) extraperitoneal (65%)
- 3) intraperitoneal (25%)
- 4) combined extraperitoneal & intraperitoneal (10%)

AAST bladder

Grade		Description
I	Hematoma	Contusion, intramural hematoma
I	Laceration	Partial thickness
II	Laceration	Extraperitoneal bladder wall laceration < 2 cm
III	Laceration	Extraperitoneal (>2 cm) or intraperitoneal (<2 cm) bladder wall laceration
IV	Laceration	Intraperitoneal bladder wall laceration >2 cm
V	Laceration	Intraperitoneal or extraperitoneal bladder wall laceration extending into the bladder neck or ureteral orifice (trigone)

What is the management of bladder injuries?

- extraperitoneal } conservative management in most cases with catheter drainage
 } cystogram at 14days prior to removal of Foley
 } Abx until 3 days after Foley removal
- intraperitoneal } open repair (intravesical approach)
 → avoid entering pelvic hematoma } stay midline
 → inspect UO for clear efflux } if injury suspected, stent or reimplant
 → JP drain
 → peri-op Abx for 3 days and then when foley removed
 → S/P drainage not necessary } urethral catheter adequate
 } cystogram after 7-10 days prior to removal of Foley

What are the indications for immediate open repair of a bladder injury?

- intraperitoneal injury
- patient undergoing laparotomy for other reasons
- penetrating or iatrogenic injury
- BN injury
- rectal or vaginal injury
- bone fragments projecting into bladder
- inadequate bladder drainage or clots in urine
- unresolving gross hematuria
- open pelvic fracture
- pelvic fracture needing ORIF

What are the signs & symptoms of unrecognized bladder injuries?

- acidosis
- azotemia
- fever and sepsis
- low u/o
- peritonitis
- ileus
- urinary ascites
- respiratory difficulties

URETHRAL INJURIES

Posterior Urethra

What are the causes of posterior urethral injury?

- 1) pelvic fractures (PFUD) } bilateral rami fractures (straddle injuries)
 } especially those resulting in vertical and rotational instability
 } 10% of males & 6% of females with pelvic #’s sustain urethral injuries
- 2) shear injuries } due to blunt trauma and stretching at membranous urethra

Which part of the posterior urethra is most often injured?

- **bulbomembranous junction** } fixed at UG diaphragm and puboprostatic ligaments
 } membranous urethral sphincter usually avulsed intact and remains functional
- in kids, injuries extend proximally to BN due to rudimentary prostate

What are the signs & symptoms suggestive of posterior urethral injury?

→ History

- inability to void
- pelvis fracture
- straddle injury
- gross hematuria

→ Physical

- blood at meatus (50%)
- palpably full bladder
- “high-riding” prostate
- “butterfly” perineal hematoma (late finding)
- inability to pass urethral catheter

What are the boundaries that define a “butterfly” hematoma?

- **must have rupture of Buck's fascia to get Butterfly distribution**
- **contained by Dartos/Colles' fascia**
- lateral } inferior pubic rami and fascia lata of thigh
- anteriorly } can go up to clavicles (dartos continuous with Scarpa's)
- posteriorly } perineal body

What is the OLD Colapinto classification of urethral injuries?

- J Urol 1977
- type I } urethral **stretch** injuries
- type II } membranous urethral **disruption proximal to GU diaphragm**
- type III } membranous urethral **disruption both proximal and distal to GU diaphragm**

What is the AAST classification of posterior urethral injuries?

- class 1 } blood at meatus, but normal imaging
- class 2 } stretch injury
- class 3 } partial disruption (contrast goes into bladder)
- class 4 } complete disruption with separation <2cm
- class 5 } complete disruption with separation ≥2cm or if concomitant vaginal, rectal, prostatic involvement

What is the Goldman classification of urethra injuries?

- Colapinto + class 4a/b and class 5
- class 1 } urethral stretch injury
- class 2 } membranous urethral disruption proximal to GU diaphragm
- class 3 } membranous urethral disruption proximal & distal to GU diaphragm
- class 4a } BN disruption into proximal urethra
- class 4b } BN disruption into bladder base
- class 5 } anterior urethral injury

How do you perform a RUG?

- unlubricated 14-16Fr catheter placed into fossa navicularis
 - gently inflate balloon until snug } can also use a Brodney clamp
 - place patient in oblique position } ~30 degrees
 - } upper leg straight, lower leg flexed at hip & knee
 - scout film
 - inject 30% contrast at 10cc increments and take film } fluoro preferred over static films
- in women with suspected urethral injury, direct urethroscopy preferred over RUG**

What is the initial management of posterior urethral injuries?

- 1) gentle attempt at placement of catheter
 - DOES NOT convert incomplete to complete injury
- 2) **S/P tube placement is gold standard**
 - S/P tube NOT CONTRAINDICATED in plated pubic symphysis
 - infection of hardware is rare
 - place S/P tube high in bladder and tunnel through skin as high as possible away from plated symphysis
 - worse outcomes if S/P only without primary realignment } if unstable, no choice
- 3) **attempt 1° realignment in stable patients**
 - NOT INDICATED for STRADDLE INJURIES
 - antegrade vs retrograde
 - avoid prolonged endoscopic realignment attempts } increases risk of infecting pelvic hematoma
 - 1° realignment decreases risk of complete stenosis, results in milder strictures, and makes future urethroplasty easier
- 4) VCUG and pericatheter RUG at 4-6 weeks } remove catheter if no extravasation
 - } most will develop stenosis
- 5) remove S/P tube once patients voids well for 7-14 days
 - some advocate open exploration + realignment with BN tears or “pie-in-the-sky” bladders
 - associated rectal injuries require open exploration, repair, irrigation, and placement of drains
 - **immediate open primary realignment NOT RECOMMENDED**
 - higher rates of ED, incontinence, stricture formation, and operative blood loss

What is the management of female urethral disruption related to pelvic fracture?

- **immediate primary repair or at least realignment over a catheter**
 - avoids subsequent urethrovaginal fistulas or urethral obliteration
 - delayed reconstruction too difficult because short urethra (4cm) not amenable to anastomotic repair when embedded in scar
- close any concomitant vaginal lacerations to prevent vaginal stenosis



→ POSTERIOR URETHRAL INJURY AT BM JUNCTION

- pelvic hematoma displaces bladder to right
- S/P tube
- normal anterior urethra

When should delayed reconstruction of a posterior urethral disruption be undertaken?

- **scar tissue stable after 3 months**
- once patient stable and ambulatory, can attempt posterior urethroplasty at this time
 - patient must be able to tolerate proper positioning for OR (exaggerated lithotomy)

What is the pre-op w/u for delayed posterior urethroplasty after posterior urethral injury?

- 1) RUG + VCUG
 - once BN opens, prostatic urethra should be visualized enabling measurement of distance between ends of disrupted urethra
 - if BN doesn't open, urethroscopy is used to assess defect
 - **appearance of BN on pre-op imaging (open or closed) DOES NOT correlate well with BN function post-op**
- 2) MRI
 - can characterize defect length and direction of dislocation

What are the definitive management options for posterior urethral injuries?

- 1) endoscopic treatments eg VIU
 - for short strictures after successful primary realignment
 - **not recommended if stricture >1cm**
 - "cut-to-light" procedures have poor results with high complication rates
- 2) posterior urethroplasty } **treatment of choice (must wait ~3months for scar to stabilize)**
 - **perineal approach is preferred**
 - must determine if prostatic urethral apex can be reached by perineal approach
 - 95% can be done via perineal approach
 - excise all scar tissue from proximal urethra until 28Fr bougie passes without resistance
 - bulbar urethra anastomosed to prostatic urethra in tension-free manner
 - **can gain length by several methods:**
 - mobilize bulbar urethra
 - separation of corporal bodies
 - inferior pubectomy
 - corporal rerouting

What are the indications for combined abdominoperineal approach (+/- partial pubectomy)?

- 1) severe fibrosis
- 2) previous failed anastomotic urethroplasty
- 3) associated BN injury
- 4) kids

What are the potential complications of posterior urethral injuries?

→ complications are mainly due to injury itself not the treatment

- 1) ED } 30-60% in PFUD
 } some degree of arterial insufficiency
 } patients with ED may be more vulnerable to restenosis after posterior urethroplasty due to bulbar urethral ischemia
 } penile arterial duplex Doppler studies may delineate candidates for penile revascularization
- 2) incontinence } 2-4%
- 3) anejaculation } 2-4%
- 4) areflexic bladder } 2-10%
- 5) fistulae
- 6) strictures
- 7) periurethral abscess
- 8) urethral diverticulum

What are the outcomes of posterior urethroplasty after posterior urethral injury?

- 12-15% have recurrent stenosis at the anastomosis
→ VIU often successful in this setting

Anterior Urethra

What are the causes of anterior urethral injury?

- usually isolated
- most are due to straddle injury involving bulbar urethra } urethral stricture disease primary morbidity in future
- penetrating injury to penile urethra less common

What is the signs suggestive of anterior urethral injuries?

- blood at meatus
- perineal hematoma
- gross hematuria
- urinary retention
- blood and urinary extravasation into scrotum } severe trauma

What is the McAninch classification of anterior urethral injuries?

- contusion
- incomplete disruption
- complete disruption

What is the initial management of anterior urethral injuries?

- 1) contusions & incomplete disruptions } urethral catheter diversion alone
- 2) complete disruption
 - major straddle injuries } S/P tube placement
 } delayed reconstruction
 - high-velocity GSWs } S/P tube placement
 } delayed reconstruction
 - low-velocity GSWs } primary surgical repair recommended
 } catheter alignment alone has high stricture rate

What is the pre-op w/u for delayed anterior urethroplasty after anterior urethral injury?

- RUG + VCUG } characterize obliterated urethra
- urethral U/S also can delineate length and severity of stricture

What are the definitive management options for anterior urethral injuries?

- straddle injury with obliterated bulbar urethra } anastomotic urethroplasty
→ >95% success rate
- partial urethral narrowing } VIU
- repeated VIU or dilation is more costly and lead to more complex reconstructive procedures
(eg requiring grafts)
- UroLume stents contraindicated in setting of traumatic urethral strictures

Chapter #84 – Lower Urinary Tract Stones

BLADDER STONES

How common are bladder stones?

- accounts for only ~5% of urinary stones in developed countries } most are asymptomatic
- **75% are due to BOO in older men**
- usually single stones, but multiple stones seen in 25-30% of cases
 - multiple stones more common in patients with bladder diverticula

What is the classification of bladder stones?

- 1) migrant } stones that pass down into bladder
- 2) primary idiopathic } rare and mainly in kids <10yrs old in under-developed countries
 - } 10x more common in boys
 - } usually solitary and don't recur once removed
 - **mostly ammonium acid urate stones +/- Ca oxalate stones**
 - } from dietary and nutritional deficiencies
 - lack of animal protein and cow's milk
 - cereal based diet
 - usually ammonium acid urate stones alone +/- Ca oxalate
 - may also contain Ca PO₄
 - Rx → mixed cereal diet + milk supplementation
- 3) secondary } related to urinary stasis or recurrent UTIs due to BOO or neurogenic bladder dysfunction
 - incomplete emptying most common finding (BPH most common cause)
 - } **most commonly uric acid or Ca oxalate or struvite (Mg NH₄ PO₄)**
 - } intestinal mucosa or FBs in GU tract increase risk also

What are the RFs for bladder stones?

- BOO
- BN stricture (eg post-RP)
- recurrent UTIs } 20-35% of bladder stones are associated w/ UTI (most commonly *Proteus*)
 - } struvite stones
- SCI } often Klebsiella-related struvite stones
- neurogenic bladder
- long-term bladder catheterization } most are struvite stones
 - } indwelling has ~9fold, CIC ~4fold increase in stones
- bladder diverticulum
- bladder augments & urinary diversions } mostly struvite stones or carbonate apatite stones
 - } uric acid stones if gastric segments used
- FBs } stents, self-induced, sutures, etc
- Schistosomiasis } 40% have stones from BN fibrosis

What types of bladder stones are found in patients with obstruction?

- uric acid
- Struvite (Mg NH₄ PO₄)
- Ca oxalate

How do bladder stones present?

- usually asymptomatic and are found incidentally
 - may present with LUTS or recurrent UTIs
 - pain in lower abdomen with referred pain down to tip of penis
- cysto is best way to Dx bladder stones } can look for strictures, BPH, or diverticulum that may need correction before or in conjunction with stone Rx

What are the management options for bladder stones?

- 1) chemolysis } Suby G solution or hemiacidrin for struvite stones
 } oral K citrate or intravesical Na HCO₃ for uric acid stones
 → rarely used now due to toxicity
- 2) SWL } patient placed prone with CBI running
 } often requires multiple treatments
 } mainly for those unfit for Sx
- 3) cystolitholapaxy } manual crushing of stones
 } high success rate but also high rate of complications (9-25%)
- 4) cystolithotripsy } pneumatic – good for large or hard stones (better than U/S or EHL)
 } EHL – higher complication rates
 } U/S – doesn't work for uric acid stones
 } laser – safe, effective, and easy but can be slower for large stones
- 5) percutaneous cystolithotomy } mainly for kids w/ narrow urethras or in patients w/ large stone burdens or multiple stones (long OR times)
- 6) open cystolithotomy } very successful and good for very large or hard stones
 } good option for failed endoscopic approach, abnormal anatomy, or concomitant open prostatectomy or diverticulectomy

What are the contraindications to cystolitholapaxy?

- small-capacity bladders
- multiple stones or stones >2cm
- hard stones
- bladder stones in kids
- small-caliber urethras

What are the contraindications to percutaneous cystolithotomy?

- hx of bladder Ca
- prior abdo or pelvic surgery
- prior pelvic rads
- active urinary or abdo wall infection
- pelvic prosthetic devices

What are the management options for stones in augments/urinary diversions?

- most stones in conduit diversions pass spontaneously
 - endoscopic lithotripsy or stone extraction is best for adults with simple augments and normal urethra and BN
 - trans-stomal approach described for continent cutaneous diversions
 - percutaneous cystolithotomy is the best option for stones in patients with narrow/obliterated BNs or urethras, small caliber stomas (eg Mitrofanoff), and large stone burdens
 - open cystolithotomy preferred for **abN anatomy, excessive stone burden or number, or after failed endoscopic approach**
- recurrence is common } 65% during 5 yrs
- prevention is key } good fluid intake, complete regular evacuation of reservoir, daily irrigation of pouch to remove mucus and crystals, eradication of urea-splitting bacteria
- routine endoscopic surveillance in active stone formers may be warranted

PROSTATIC AND SV STONES

What are prostatic stones?

- **calcified material on corpora amylacea**
 - **mainly Ca PO₄ trihydrate & carbonate stones**
 - proteins, cholesterol, and citrate compose 20% of stones
 - usually incidental finding
 - found in 5% of men } usually men >50yrs old
 - may be related to **infections, ochronosis, prostatic RADs, TURP, prostate stents, TB**
- Rx → no treatment indicated in most
→ TUR or simple prostatectomy for those with symptoms or intractable infections

What are SV stones?

- very rare } nucleus composed of **epithelial cells covered by lime salts**

URETHRAL STONES

How common are urethral stones?

- rare, especially among women
 - most urethral stones in women are associated with diverticula
- native or migrant stones
- **native stones** don't usually cause acute symptoms due to slow development and growth
 - **usually struvite or Ca PO₄ or Ca carbonate**
- **migrant stones are the more common } mainly Ca oxalate & Ca PO₄**
- often get impacted at prostatic urethra, bulb, proximal penile urethra, fossa navicularis, meatus

What are the RFs associated with urethral stones?

- strictures
- congenital or acquired diverticula
- chronic infection
- FBs
- schistosomiasis
- use of hair-bearing skin for urethroplasty

What are the management options for urethral stones?

- depends on size and location of stone and condition of urethra
- S/P tube if in AUR
- 1) urethral xylocaine jelly and milking of stone
- 2) urethoscopic lithotripsy and removal of fragments
- 3) meatotomy } for fossa or meatal stones
- 4) dilation and VIU + stone extraction } for concomitant strictures
- 5) external urethrotomy } for chronically impacted stones
- 6) diverticulectomy and stone removal

PREPUTIAL STONES

What are preputial stones?

- very rare } mainly in underdeveloped countries only
 - mainly in adults and associated with phimosis, poor genital hygiene, and low SES
 - key factors include obstruction with stasis, infection with alkalinization, and presence of foreign body (smegma)
 - **struvite stones, inspissated smegma stones, Ca oxalate stones**
- Rx → circumcision and stone removal
→ if left untreated, may result in chronic inflammation and urinary fistula formation

OTHER

What are the causes of stones in children?

→ INTRINSIC

- 1) genetic causes
 - AD } distal RTA (nephrocalcinosis & stones in 70%)
 - AR } cystinuria
 - } primary hyperoxaluria
 - } xanthinuria
 - } dihydroxyadeninuria
 - X-linked } Lesch-Nyhan
 - } Dent's disease (stones, hypercalciuric hypophosphatemic rickets, LMW proteinuria with nephrocalcinosis)
 - polygenetic
- 2) urinary constituents
 - hypercalciuria
 - infections
 - hyperoxaluria
 - cystinuria
- 3) stasis or UTI
 - anatomic abN'ities } UPJO most common anatomic lesions causing stones
 - functional abN'ities } MMC, neurogenic bladder
- 4) medical causes
 - bowel disease } diversion, diarrhea (dehydration)
 - metabolic acidosis (hypocitraturia)

→ EXTRINSIC

- 1) low birth weight (<1.5kg)
 - 30-90% of very LBW babies treated with lasix have stones
 - can occur in kids that have not received lasix
- 2) diet
 - protein/fat
 - salt
 - alkaline-ash (vegetarians with alkaline urine)
 - acid-ash (meat eaters with acidic urine)
- 3) meds
 - stone-forming meds } triamterine, silicate antacids, indinavir
 - stone-facilitating meds } probenecid, salicylates
 - lasix
 - Na, Ca, or vit D supplementation
 - steroids
 - theophylline
 - TPN } increases oxalate excretion in LBW babies

List causes of stones in neonates }}} “DUTTCH Stones in Really Little Suckers”

- **D**ehydration
- **U**nderweight at birth
- **T**PN
- **T**heophylline
- **C**ystinuria
- **H**yperPTH'ism (congenital)
- **S**teroids
- **R**TA (distal)
- **L**asix
- **S**epsis

Chapter #85 – Molecular Biology, Endocrinology, and Physiology of the Prostate & SVs

DEVELOPMENT AND CELL BIOLOGY

What are the sex accessory glands in the human male?

- prostate
- SVs
- ampullary glands
- bulbourethral glands (Cowper's)
- glands of Littre

Name the major substances produced by the male sex accessory glands.

- PG's (200µg/mL)
- fructose (2mg/mL)
- spermine (3mg/mL)
- citric acid (4mg/mL)
- proteins (40mg/mL) } immunoglobulins, human kallekriens, semenogelins, etc
- enzymes } proteases, esterases, phosphatases, etc

What is the function of seminal fluid?

- involved in clotting & lysing process
- increasing sperm motility or survival (nutrition, etc)
- enhancing sperm transport in male & female reproductive tracts
- extend viability of sperm
- decrease environmental shock to sperm (block pathogens, etc)

What is the embryologic origin of the male sex accessory glands?

- | | | | |
|----------------------|------------------------------------|-----|---|
| - Wolffian ducts | } efferent ductules | \ / | - development stimulated by fetal testosterone (not DHT) |
| | } epididymis + appendix epididymis | | |
| | } vas deferens + ampulla of vas | | |
| | } ejaculatory ducts | | - complete by week 13 |
| | } SVs | | |
| | } CZ of prostate | / | |
| - mesodermal buds | } inner zone of prostate | \ / | - invade mesenchyme on either side of verumontanum |
| - endodermal buds | } outer zone of prostate | | - stimulated by DHT |
| | | | - starts at 3 rd month & complete by 4 th |
| - mullerian remnants | } prostatic utricle | | |
| | } appendix testis | | |

What are the key points in prostate development?

- stimulated by DHT
 - epithelium makes most of DHT } AR type 1 in epithelium, AR type 2 (main) in stroma
 - stroma/mesenchyme has the androgen receptors necessary for proper development
 - in response to DHT-AR binding, stroma makes growth factors that drives epithelial development (EGF, IGF, TGF, KGF, FGF, etc)
- prostate forms acini & collecting ducts by arborizing into urethra from the UG sinus
- growth occurs primarily on tips, as ducts extend & branch during development
- MIS must be present (Sertoli cells) for ipsilateral regression of mullerian duct structures

What genes are involved in prostate development?

- sonic hedgehog protein (shh)
 - forkhead box A1 (foxA1)
 - NKX3.1
- \ } homeobox proteins
/

What is the role of sex hormones on post-natal prostate development?

- stimulation of postnatal development is under control of residual maternal steroids (estrogens)
- postnatal prostatic involutional phase (first 5 months after birth)
- neonatal surge of T seen b/w 2 & 3 mos of age } levels rise to 60x normal prepubertal level
(can reach adult levels – 400ng/dL)
- initially high estradiol levels quickly fall off } nearly undetectable within first few days
} neonatal estrogens are important in long-term growth of prostate (imprinting)
} involves mainly ER- α receptors in stroma
- initially high progesterone levels are from placenta } second surge seen at ~2months of age

What are the different cell types within the prostate?

1) **epithelial cells**

- basal/stem cells } only account for 10% of prostate cells
→ not affected by androgen ablation
- neuroendocrine cells } between columnar secretory epithelial cells
→ open vs closed types
→ DO NOT stain for PSA, androgen receptor
- transit-amplifying (proliferating) } found in basal layer and develop from stem cells
- columnar secretory } terminal differentiated epithelial cells (**MOST COMMON**)
→ decrease in # and size with androgen ablation
} **stain for PSA, PAP, androgen receptor, keratins**

2) **stromal cells**

- smooth muscle cells } have $\alpha 1A$, $\alpha 1B$, and $\alpha 1D$ adrenergic receptors
- fibroblasts

3) **tissue matrix**

- extracellular matrix (BM, connective tissue, GAG) \
 - membrane matrix \
 - cytomatrix /
 - nuclear matrix /
- fibronectin
- laminins interact with
type 4 collagen of BM

What is the function of prostatic laminins?

- surrounds BM of prostate acinar epithelial cells, capillaries, smooth muscle, and nerve fibers
- interact with type 4 collagen of BM
- adhesion
- proliferation
- differentiation
- growth
- migration

Table 85-1 -- Summary of the Anatomy and Cell Biology of the Prostate Gland

Components		Properties
<i>Development</i>		
Seminal vesicles		From wolffian ducts through testosterone stimulation
Prostate		From urogenital sinus through dihydrotestosterone stimulation
<i>Prostate zones</i>		
Anterior fibromuscular		30% of prostate mass, no glandular elements, smooth muscle
Peripheral		Largest zone, 75% of prostate glandular elements, site of carcinomas
Central		25% of prostate glandular elements, surrounds ejaculatory ducts, may be of wolffian duct origin, seminal vesicle-like
<i>Preprostatic transition</i>		
		Smallest, surrounds upper urethra complex, sphincter
		5% of prostate glandular elements, site of benign prostatic hyperplasia
		15% to 30% of prostate volume
<i>Epithelial cells</i>		
Basal		Small undifferentiated, keratin-rich (types 4, 5, 6) pluripotent cells; less than 10% of epithelial cell number
Transient proliferating		Incorporate thymidine
Columnar secretory		Terminal differentiated, nondividing, rich in acid phosphatase and prostate-specific antigen; 20 m tall, most abundant cell; keratin types 8, 18, 19
Neuroendocrine		Serotonin rich, APUD type
<i>Stroma cells</i>		
Smooth muscle		Actin-rich, myosin
Fibroblast		Vimentin rich and associated with fibronectin
Endothelial		Associated with fibronectin, alkaline phosphatase positive
<i>Tissue matrix</i>		
<i>Extracellular matrix</i>		
	Basement membrane	Type IV collagen meshwork, laminin rich, fibronectin
	Connective tissue	Type I and type III fibrillar collagen, elastin
	Glycosaminoglycans	Sulfates of dermatan, chondroitin, and heparin; hyaluronic acid
Cytomatrix		Tubulin, actin, and intermediate filaments of keratin
Nuclear matrix		DNA tight-binding proteins, RNA and residual nuclear proteins

→ ANATOMY & CELL BIOLOGY OF THE PROSTATE GLAND

ENDOCRINE CONTROL OF PROSTATE GROWTH

What happens to testosterone in the human body?

- synthesized from pregnenolone (Leydig cells) } reversible process
- T can be converted to DHT (5 α -reductase) } irreversible
- T can be converted to estrogens (aromatase) } irreversible

Describe the endocrinology of the prostate.

- hypothalamus makes GnRH (LHRH)
- LHRH stimulates pituitary to release LH
 - LHRH agonists/antagonists block LH release from pituitary
- LH stimulates Leydig cells in testis to make T
- T converted peripherally by aromatase into estrogens
 - DES blocks LH release by negative feedback on pituitary
- pituitary also releases ACTH
- ACTH stimulates adrenal gland to produce androstenedione
 - complete androgen blockade to block adrenal androgens
 - androstenedione can also be converted peripherally into T } can also be converted by aromatase into estrogen

Where is testosterone made?

- >95% is made in testis (Leydig cell)
 - testis makes 6-7 mg/day
 - spermatic vein [T] is ~75x higher than in peripheral venous serum
- <5% is made from adrenals
 - androstenedione converted peripherally into T and estrogen
 - DHEA also converted into T } accounts for <1% of total plasma T

What is the half life of testosterone?

- testosterone $T_{1/2}$ = 10-20 minutes

What is a “normal” testosterone level?

- 10 to 34 nmol/L } 300 to 1000 ng/100mL (avg ~600)
 - DHT concentration in serum is >10x lower (~50 ng/100mL)
- 2% is free T } only free T is available for conversion to DHT in the prostate or for conversion to 17-ketosteroids in liver & intestines
- 38% bound to albumin } bioavailable T = free + albumin-bound
- 60% bound to SHBG

Which androgens are made by the testis?

- testosterone
- androstenediol
- androstenedione (can't be converted to DHT)
- DHEA
- DHT

What is the function of 5 α -reductase?

- converts T into DHT
- 5AR type 1 } found mainly in skin and scalp (small amount in prostate epithelium)
 - on chromosome 5
 - dutasteride acts on 5AR type 1 & 2
- 5AR type 2 } found mainly in prostate stroma & accessory sex glands
 - on chromosome 2
 - this isoform is mutated in 5-AR deficiency
 - finasteride acts on 5AR type 2 only

	Type I	Type II
<i>Human</i>		
Chromosome	5p15	2p23
Molecular weight	29,000	28,000
Amino acids	259	254
Exons	4	4
Introns	5	5
Homology	49%	49%
pH optima	Alkaline (6–8.5)	Acidic (5.0)
K _m testosterone (μ M)	1.5	0.1–1.0
K _i finasteride (nM)	325	12
Half-life, hour	20–30	20–30
5α-Reductase deficiency	Normal	Mutated
Prostate cells		

→ PROPERTIES OF 5α-REDUCTASE TYPES I AND II

Why is DHT not a significant systemic androgen?

- potent androgen (1.5x to 2.5x as potent as T) but ...
- low plasma concentration (>10x lower than T) and tightly bound to plasma proteins

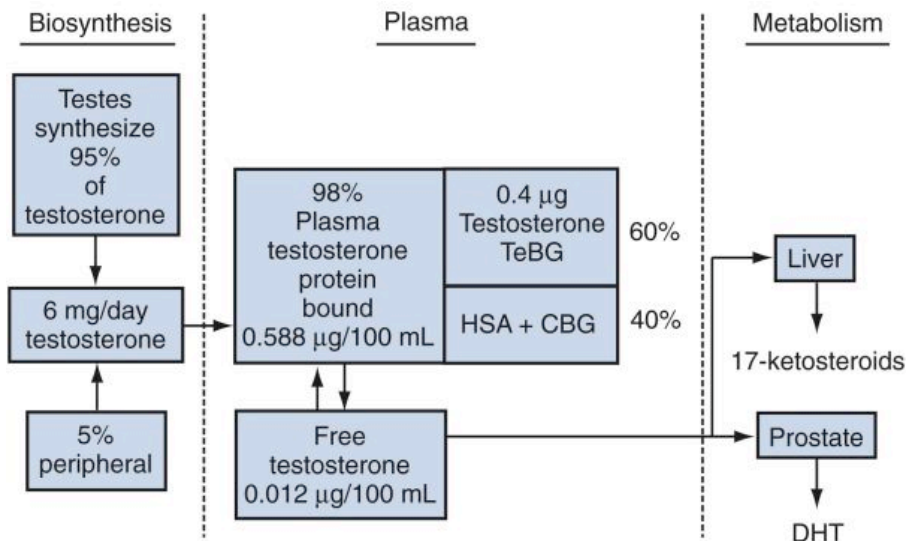
Why is DHT a significant androgen WITHIN the prostate?

- **DHT has 5x higher concentration than T inside prostate gland**

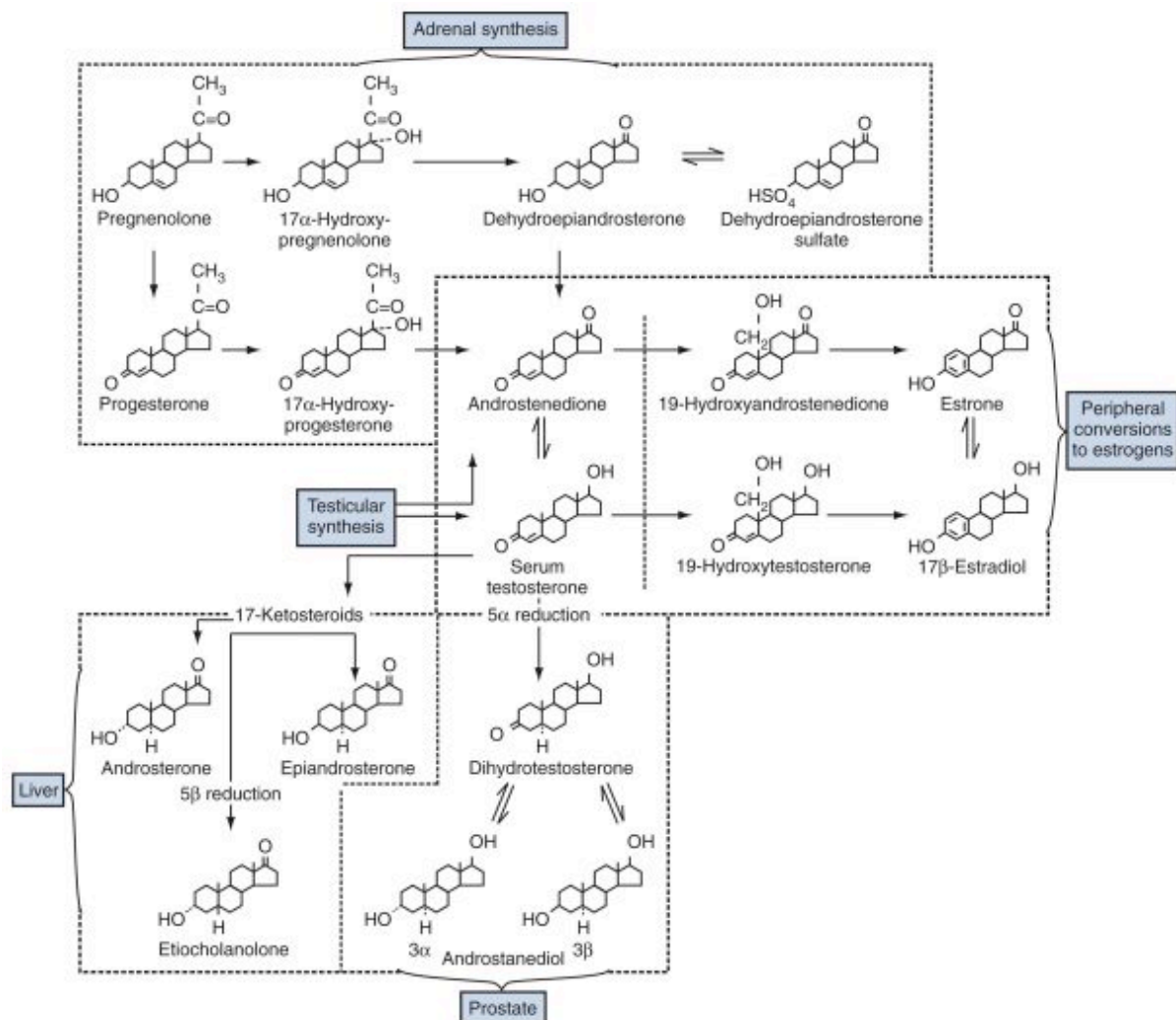
Which androgens are made by the adrenal?

- testosterone
- androstenedione (can't be converted to DHT)
- DHEA
- DHEAS
- progesterone

} adrenal androgens do not have significant impact on prostate tissue



→ TESTOSTERONE PHYSIOLOGY



→ TESTOSTERONE SYNTHESIS & METABOLISM

Which plasma proteins bind to T?

- 2% free
- 38% bound to albumin (low affinity, high capacity due to abundance)
- ~60% bound to SHBG (high affinity, low capacity due to low concentration)
- nominal amounts also bound to
 - } corticosteroid-binding globulin (transcortin)
 - } progesterone-binding globulin
 - } α -acid glycoprotein

Where are estrogens made in men?

- estradiol production in men is 40 to 50 μ g/day
- 75-90% comes from peripheral conversion of androstenedione (to estrone) and T (to estradiol)
 - only ~1% of total androgens is converted to estrogens peripherally
 - adipose tissue
- 10-25% accounted for by direct testis secretion
 - Sertoli cells

How does estrogen affect serum T levels?

- 1) -ve feedback on pituitary } decreases LH secretion (affects Leydig cell production of T)
- 2) increases SHBG levels } decreases free T levels
 - estrogen can also bind to SHBG but has 3x lower affinity

What is the role of prolactin in prostate physiology?

- small role } supportive role in zinc & androgen uptake and metabolism
- } may play role in BPH

REGULATION OF PROSTATE GROWTH BY STEROIDS & PROTEIN GROWTH FACTORS

What are the 7 main factors that affect prostate growth regulation?

- 1) endocrine factors (systemic signal)
 - eg serum T, estrogens, prolactin, etc
- 2) neuroendocrine signals
 - eg serotonin, acetylcholine, NE
- 3) paracrine factors (neighbouring cells)
 - eg growth factors (EGF, FGF)
- 4) autocrine factors
 - GFs released by cell then feed back on same cell
- 5) intracrine factors
 - similar to autocrine factors but work inside cell
- 6) extracellular matrix factors
 - eg GAG, integrins, cell adhesion molecules
- 7) cell-cell interactions
 - between epithelial and/or stromal cells
 - eg E-cadherin

What is the fate of T once it reaches the prostate epithelial cell?

- free T enters prostate cell by diffusion
 - } 90% converted to DHT by 5-AR → irreversible
 - } also metabolized to diols (3α and 3β) → reversible
 - } also metabolized to inactive triols (6α and 7α) → irreversible

How do estrogens regulate prostate growth?

- systemically, estrogens decrease T levels
- locally, at physiologic levels, estrogens synergize androgen effects and stimulate growth mainly in prostatic stroma
- estrogens can cause florid squamous cell metaplasia in prostate growth } offset by androgens

What are andromedins?

- key stromal growth factors produced by DHT stimulation
 - tissue remodeling enzymes
 - cytokines
 - hormones
 - growth factors
- \ responsible for wound healing, maintaining cell
/ turnover (proliferation & apoptosis), and
/ epithelial cell differentiation

What are the 4 types of cell adhesion molecules?

- 1) integrins (link cell to BM and extracellular matrix)
- 2) cadherins (link cell to neighbouring cells)
- 3) selectins
- 4) immunoglobulin superfamily adhesion molecules

REGULATION OF PROSTATE GROWTH AT THE MOLECULAR LEVEL: STEROID RECEPTORS

What is the role of vitamin A and D in prostatic function?

- Vit A } retinoids may be involved in the **inhibition of growth of normal & PCa cells**
 - } there are ≥6 human retinoid receptors ie RAR (α , β , γ) and RXR (α , β , γ)
 - steroid receptor superfamily
 - } retinoids may down regulate AR expression in the prostate
 - fenretinide (4-HPR) and 9-cis-retinoic acid
- Vit D } blocks proliferation of LNCaP & PC-3 cells via IGF-binding protein 6 upregulation
 - } causes epithelial growth & stromal atrophy in normal prostate tissue
 - overall, enhances growth

What is the function of the androgen receptor (AR) in the prostate?

- AR is a cytoplasmic steroid-binding protein } gene found on chromosome Xq11
 - } member of nuclear receptor superfamily
- 5000 to 20,000 AR's found per cell in prostate and SV } only ~400 AR response elements
- DNA-binding domain is **rich in cysteine & zinc fingers**
- 1) genomic function } certain transgenes are regulated by activated AR
- 2) non-genomic function } regulates rapid changes in cellular physiology

How does the androgen receptor (AR) work within the prostate?

- 1) DHT or T binds to specific ARs in cytoplasm
 - AR is activated by post-translational modifications (eg phosphorylation)
- 2) activated AR receptor (bound to DHT) is actively translocated into nucleus (NL1 & NL2)
 - process involving at least 2 nuclear localization signals
- 3) interaction of AR w/ co-activators or co-repressors results in gene activation or repression
 - ATP-dependent chromatin remodeling via SW1-SNF complex
 - histone acetyltransferase-dependent process also involved
- 4) binding of activated AR-co-activator complex to androgen response elements (DNA)
 - activated AR acts as transcription factor when bound to DNA & nuclear matrix
 - nuclear matrix serves as important structural modulator of nuclear regulation
 - gene regulation via increased RNA polymerase II transcription of mRNA
- 5) stabilized mRNA is then transported into cytoplasm
 - ribosomes translate mRNA in to proteins
- 6) proteins available for secretion (eg PSA)

GROWTH FACTORS & GROWTH SUPPRESSORS

Name the different GROWTH FACTORS involved in prostate physiology.

- stromal & epithelial cells can make & respond to growth factors } reciprocal & interactive
- many growth factors are under hormonal regulation } androgens, estrogens, etc
- bFGF (high in BPH) } potent stromal mitogen but weak epithelial mitogen
- EGF (high in BPH and PCa)
- TGF- α (high in PCa)
- TGF- β (high in BPH)
- MIS
- IGF
- PDGF

Which growth factors are capable of inducing bone formation (osteoblastic)?

- TGF- β 1
- TGF- β 3
- BMP2,3,4,6 (bone morphogenic protein)

What are the 3 sources of NO in the prostate?

- 1) nerve (nNOS)
- 2) immune cells eg macrophages (iNOS)
- 3) endothelial cells (eNOS)

REGULATION OF PROSTATE GROWTH: BALANCE OF CELL REPLICATION & CELL DEATH

What is the role of telomerase in cancer cells?

- telomere length dictates cell life span } once shortened, scheduled for apoptosis
- stem cells & germ cells can overcome this Hayflick limit by the enzyme telomerase
- telomerase can add TTAGGG repeats back on to telomere } reverse transcriptase activity
 - prevents shortening and subsequent apoptosis and cell death
- cancer cells also have telomerase and can thereby avoid apoptosis and cell death

What are the stages of cell cycle?

- 1) interphase } G1 phase, DNA synthesis (S) phase, G2 phase
- 2) mitosis (M) } prophase, metaphase, anaphase, telophase

What are the roles of checkpoint proteins in the cell cycle?

- 1) ensure cell does not start mitosis until DNA replication & DNA damage repair is complete
- 2) ensure chromosomal segregation occurs along intact mitotic spindle
- 3) ensure key processes of metabolism & homeostasis are coordinated within various stages of the cell cycle (G1, S, G2, M)

PROMINENT, NONPEPTIDE COMPONENTS OF PROSTATIC SECRETIONS

What are the components of human semen?

- avg volume is 2-6mL
- 1) spermatozoa (<1% of total ejaculate) } ~100 million per mL
- 2) seminal plasma } SVs contribute the most volume (50-75%)

What are the main non-peptide components of seminal plasma?

- SV secretions (1.5-2mL) } fructose (200-300 mg/dL)
 - } Prostaglandins (PG-A, PG-B, PG-E, and PG-F)
 - SVs are the richest source of PGs
- prostatic secretions (0.5mL) } citric acid (500-1000x serum concentration)
 - } Zinc (140 µg/mL)
 - prostate has highest [zinc] of any organ
 - } polyamines eg spermine, spermidine
 - } phosphorylcholine
 - } cholesterol & lipids

PROSTATIC SECRETORY PROTEINS

List the major secretory proteins of the prostate gland and SVs.

→ PROSTATE

- 1) PSA (hK3) } serine protease (33kD glycoprotein)
 - } lyses clotted ejaculate
 - } concentration in semen is 1 million-fold higher than serum (mg/mL vs ng/mL)
- 2) hK2 } cleaves proPSA to generate active PSA
 - } ?marker of PCa
- 3) hK-L1 } serine protease
 - } also found in testes, breast, adrenal, uterus, thyroid, salivary glands
- 4) hK11 } serine protease
 - } ?marker of PCa
 - } also found in breast, ovary, CSF
- 5) PAP } 102kD glycoprotein
 - } 200x more abundant in prostate tissue than other tissue
 - } minor elevations in serum acid phosphatase seen w/ bone disease (metastatic PCa, Paget's disease, osteoporosis, non-PCa bone mets)
- 6) prostate-specific transglutaminase (eg TGM-4)
- 7) prostate specific membrane antigen } type 2 integral membrane protein
 - (PSMA) } structure is identical to glutamate carboxypeptidase 2 & folate hydrolase 1
 - } also found in kidney, testis, ovary, brain, liver, spleen, salivary gland, bowel, breast, skeletal muscle
 - } ?marker of PCa (may be involved w/ signal transduction to promote cell survival, proliferation, and migration)
- 8) prostate stem cell antigen } PCa-associated tumour antigen
 - (PSCA) } ?marker of PCa
- 9) PSP-94 } aka β -microseminoprotein or β -inhibin
 - } inhibits FSH
 - } also found in antrum of stomach
- 10) immunoglobulins } human IgG
- 11) C3 complement } ?marker of PCa
- 12) transferrin } carries iron through blood

→ SVs

- 1) semenogelins 1 and 2 } causes ejaculate to clot (comes mainly from SVs)
 - } degraded by PSA to various active peptides that are involved in sperm capacitation
 - } also serve as substrates for transglutaminase 4 (TGM-4)

How many different human kallikreins exist?

- **there are >15 human kallikreins** } genes located on chromosome 19
- hK3 (PSA)
- hK2 } 20,000-fold greater protease activity than PSA
 - } cleaves pro-PSA to generate active PSA
 - } elevated in PCa
- hK-L1 (KLK-L1)

What forms of PSA are found in serum?

- free (active)
- bound } α 1-antichymotrypsin (PSA-ACT)
 - } α 2-macroglobulin (PSA-A2MG) → undetectable
 - } α 1-protease inhibitor (PSA-API)

What are some ectopic sources of PSA? } } } “BALKS”

- normal & malignant breast tissue
- breast milk
- female serum
- adrenal carcinomas
- glands of Littre
- renal carcinomas
- Skene's gland tumours

What are the sources of semenogelin?

- **SV (main source)**
- prostate
- epididymis (only semenogelin I)
- vas deferens
- trachea
- skeletal muscle
- CNS

COAGULATION & LIQUEFACTION OF SEMEN

What are the major factors responsible for semen coagulation?

- unrelated to blood coagulation factors } fibrinogen, factor 12, prothrombin (factor 2), etc
- semenogelin

What are the major proteolytic enzymes in semen?

- 1) **PSA**
- 2) **plasminogen activators**
- 3) pepsinogen
- 4) lysozyme
- 5) α -amylase
- 6) hyaluronidase

PROSTATIC SECRETIONS & DRUG TRANSPORT

Name drugs or compounds that can concentrate in prostatic tissue?

- pass into tissue by diffusion
- ethanol
- iodine
- antibiotics } macrolides (erythromycin)
 } sulfonamides
 } tetracycline
 } clindamycin
 } TMP
 } fluoroquinolones
 } chloramphenicol

What is the pH of ejaculated semen?

- fresh semen is slightly **alkaline (7.3-7.7)**
 - SV secretions are alkaline
 - however, prostatic secretions are acidic

Ejaculate components and source

Source	Volume	Components
Testes	< 1%	Sperm
SV	1.5 – 2 mL	Fructose, PGs, base (EDO = acid semen) coagulation factors
Prostate	0.5 mL	Zn, citrate, PSA, acidic (coagulum lysis)
Cowper's and Littre glands	0.1 – 0.2 mL	Liquefaction factors

Chapter #86 – BPH

ETIOLOGY AND PATHOPHYSIOLOGY

What is BPH?

- increased # (hyperplasia) of epithelial & stromal cells in periurethral area of the prostate (TZ)
→ histologic Dx
- **either due to epithelial & stromal proliferation OR to impaired programmed cell death leading to cellular accumulation**
- stroma (smooth muscle and ECM) and epithelial cells

List factors that contribute to the development of BPH

→ “FAE SIGN”

- 1) Family Hx } AD inheritance pattern
 } familial BPH have larger glands
- 2) Androgens } cause cell proliferation but also inhibit rate of cell death
 } DOESN'T cause BPH but androgens are REQUIRED for BPH
- 3) Estrogens } inhibits cell death
 } may upregulate AR levels in prostate
- 4) Stromal-epithelial interactions } stromal & epithelial cells maintain paracrine communication
 } defect in stromal cell protein may result in loss of signal for apoptosis
- 5) Inflammation } cytokines may upregulate cell proliferation of stromal cells
- 6) Growth factors } interaction with steroid hormones may lead to cell proliferation or decreased levels of apoptosis
- 7) Neurotransmitters } sympathetic pathways may promote hyperplastic growth

Is BPH inheritable?

- 1st degree relative with BPH gives you a HR of ~4 in comparison to those with no family hx
- AD pattern of inheritance
- if <60yrs of age, likely 50% is genetic
- if >60yrs of age, only ~10% can be attributable to a genetic cause

Which androgens affect prostate tissue?

- **DHT } 90% of total prostatic androgen**
 } converted by 5 α -reductase from testicular testosterone
 } **intraprostatic DHT levels are maintained but NOT elevated in BPH**
 → has to do with maintained AR levels too
- testicular androgens } less potent than DHT in prostate because of lower affinity for AR
- adrenal androgens } only 10% of total prostatic androgen and has limited role in BPH

How does the prostate differ from other androgen-dependent organs?

- brain, penis, skeletal muscle, seminiferous epithelium, SVs
- prostate maintains ability to respond to androgens
- AR levels remain high throughout life } may even be higher in hyperplastic tissue

What types of 5α -reductase enzymes are described?

- type 1 } predominant enzyme in extraprostatic tissue (**skin, liver**)
 - made in prostate also (**epithelium**)
 - } still made in 5α -reductase deficiency syndrome
 - } inhibited by dutasteride only
- type 2 } predominant **prostatic** enzyme (**stromal**)
 - } also expressed outside prostate
 - } involved in 5α -reductase deficiency syndrome
 - } inhibited by BOTH finasteride and dutasteride

Which growth factors have been implicated in BPH?

- VEGF
 - bFGF (FGF-1)
 - acidic FGF (FGF-2)
 - Int-2 (FGF-3)
 - **KGF (FGF-7)**
 - EGF
 - IGF
 - TGF- β }
- \ } cell proliferation
/
/ }
- } apoptosis

What is the pathophysiology of BPH?

- prostatic hyperplasia increases urethral resistance, resulting in changes in bladder function
- obstruction-related changes in detrusor function, in addition to age-related changes, result in changes in both bladder & nervous system function
- first develops in periurethral TZ of the prostate (**mainly stromal, but not exclusively**)
- presence of prostatic capsule leads to development of LUTS from transmitted “pressure” on urethra
 - TUIP improves LUTS without debulking adenoma
- size of prostate DOES NOT correlate with degree of obstruction

What are the histologic features of BPH?

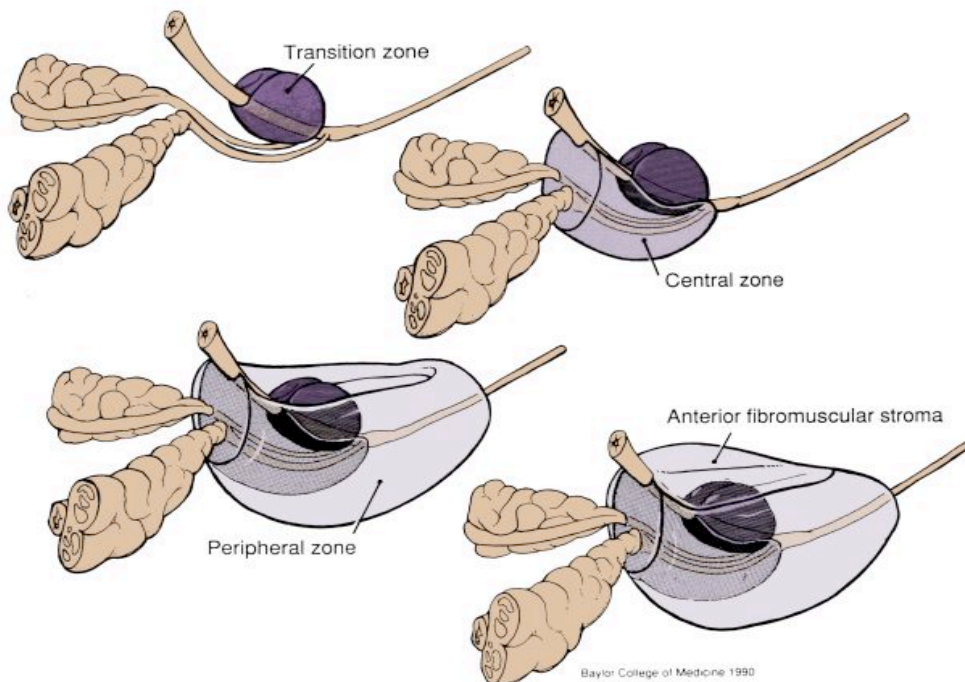
- true hyperplasia } increased number of cells
- early periurethral nodules are purely stromal in character } stromal nodules are smaller than glandular nodules seen in TZ
- early TZ nodules are proliferation of glandular tissue
- contains large amount of smooth muscle } upregulated non-muscle myosin heavy chains & downregulation of smooth muscle myosin heavy chain
 - } adrenergic system upregulates smooth muscle contractions

What are the main changes seen in the bladder in response to BPH/BOO?

- 1) detrusor instability or decreased compliance
 - 2) decreased detrusor contractility
- increase in detrusor collagen

List 5 histologic types of BPH nodules.

- **fibroadenomyomatous (most common to have all components)**
- fibroadenomatous
- muscular
- fibromuscular
- stromal



Transition zone } surrounds urethra proximal to ejaculatory ducts

Central zone } surrounds ejaculatory ducts & projects under bladder base (**only zone of Wolffian origin**)

Peripheral zone } constitutes bulk of the apical, posterior, & lateral aspects of the prostate

Anterior fibromuscular stroma } extends from the BN to striated urethral sphincter

EPIDEMIOLOGY AND NATURAL HISTORY

What is the prevalence of BPH?

- difficult to define due to lack of globally accepted epidemiological definition
- can assess by histologic criteria } presence of stromoglandular hyperplasia
 - } 40% by age 50, 80% by age 80
- can also assess by clinical criteria } more difficult because definition of BPH varies
 - } symptoms (IPSS) or enlargement of gland or presence of obstruction
 - **IPSS increases with age**
 - **prostate size on TRUS ↑'s slowly but steadily w/ age**
 - **pressure-flow studies would be ideal to assess BOO**
 - but too invasive so Qmax often used**

What epidemiologic factors have been associated with BPH?

- high income groups associated with higher rates of BPH
- lower income groups associated with higher rates of Sx for BPH
- decreased level of sexual activity and ED have been associated with BPH
 - likely confounding effects of age
 - with increasing age, rate of ED increases and sexual activity decreases
- alcohol & cirrhosis have been associated with lower rates of BPH
 - alcohol decreases testosterone levels
- HTN has been associated with BPH
- smoking has been associated with BPH
 - nicotine increases testosterone
- obesity associated with BPH and increased rates of Sx for BPH

Which medications exacerbate BPH?

- cold meds with α -sympathomimetics
- antidepressants
- antihistamines
- bronchodilators

How well do various measures of BPH and LUTS correlate?

- modest correlation at best
- serum PSA and prostate volume moderately correlate } depends on age and ethnic origin
- **symptoms, Qmax, prostate volume DO NOT predict presence or degree of obstruction**

What is the natural history of BPH?

- ~40% of men with LUTS improve or stabilize and do not need to have Sx
- ~25% of men on conservative WW go on to need Sx
- ~10% of men undergoing Sx had treatment failures
- MTOPS showed ~15% of placebo arm had worsening of symptoms over 4yrs
- PLESS showed that a higher PSA predicts men whose symptoms will worsen
- symptoms tend to progress more in older men

List potential complications of BPH

- overall rare
- affect on lifestyle and QOL is the usual main complication of BPH
- mortality } rare and decreasing
- bladder stones } <1% and therefore no need for screening for stones unless indicated
eg stuttering of urination, hematuria
- UTIs } <1% and increased PVR has not been shown to be a clear risk factor
} MTOPS showed that it occurs in 0.1 per 100 patient yrs in placebo arm
- bladder decompensation } delayed treatment may result in the development of some degree
of bladder decompensation
- incontinence } found in ~5%
- upper tract deterioration } found in ~2.5%
} associated with increased complications after TURP & mortality
- hematuria } occurs in ~2.5%
- AUR } 75% undergo Sx after spontaneous AUR, whereas only 25% undergo Sx after precipitated AUR
} occurs in ~2-5%
} accounts for 5-30% of the indications for Sx

What are the RFs associated with the development of AUR?

- spontaneous
 - increased age
 - worse LUTS
 - lower Qmax (<12cc/s)
 - prostate >30g
 - higher PSA
- precipitated
 - UTI
 - bladder overdistension
 - excessive fluid intake
 - EtOH
 - sexual activity
 - debility
 - bed rest
 - prostatic infection
 - non-prostate-related surgery
 - meds (adrenergic or anticholinergic)

List the RFs associated with BPH progression

- age
- high baseline bother score
- high IPSS score
- low baseline Qmax
- large prostate
- higher PSA

What are the most significant RFs associated with the need for BPH-related Sx?

- advanced age
- increased prostate size

Chapter #87 – BPH: Medical Management

What is the initial w/u for LUTS?

- 1) History (MANDATORY)
 - characterize LUTs } onset, duration, associated symptoms, alleviating, aggravating, etc
 - complications } hematuria, UTI, stones, AUR
 - fluid intake, previous treatment
 - AUA symptom score is essential for baseline & prognosis } “FUNWISE” - score out of 35
 - +/- voiding diary
 - PMHx } DM, nervous system disease, strictures, AUR, bowel dysfxn, STDs
 - meds, allergies, FmHx, smoking, EtOH, drugs
- 2) Physical exam (MANDATORY)
 - general appearance, vitals (BP)
 - abdo exam
 - DRE } size of gland, nodules, tone, etc
 - external genital exam } phimosis, meatal stenosis, urethral mass, etc
 - focused neuro exam } bulbocavernosus reflex, peripheral exam
- 3) urine tests (MANDATORY)
 - urinalysis + urine C&S } to r/o hematuria and UTI
 - cytology if severe irritative LUTS, esp if +ve smoking hx (NOT RECOMMENDED by CUA)
- 4) bloodwork
 - serum creatinine is OPTIONAL } if measured & elevated, imaging is indicated
 - PSA is RECOMMENDED ONLY IF RELEVANT } patient with life expectancy >10yrs
- 5) +/- ancillary tests (not routinely recommended)
 - uroflowmetry + PVR if moderate to severe symptoms
 - consider UDS or cysto based on work-up } hematuria, strictures, suspicious for Ca, prior Sx, mixed storage & voiding symptoms, etc
 - upper tract imaging based on work-up } hematuria, UTIs, renal failure, stones, etc

DIAGNOSIS

What are the CUA Guidelines on the initial w/u for LUTS?

- mandatory } History & Physical (including DRE + focused neuro exam)
- } urinalysis
- recommended } AUA symptom score (IPSS)
- } PSA (if ≥10yr life expectancy and if it may change management)
- optional } uroflow & PVR
- } creatinine
- } voiding diary
- } sexual function questionnaire (eg IIEF-5)
- NOT recommended } cytology } TRUS
- } cysto } upper tract imaging
- } UDS } prostate bx

What are the AUA Guidelines on the initial w/u for LUTS?

- | | | |
|---|---|--|
| → Recommended <ul style="list-style-type: none"> - Hx & Physical - Urinalysis - IPSS - PSA (if indicated) | → Optional <ul style="list-style-type: none"> - uroflow & PVR - cytology - other LUTS questionnaires | → Not Recommended <ul style="list-style-type: none"> - creatinine |
|---|---|--|

What is the AUA symptom score?

- validated questionnaire developed in 1992
- can't be used to Dx BPH
- good to assess baseline symptom severity, response to Rx, and detect progression
- 7 questions } frequency, urgency, nocturia, weak stream, intermittency, straining, incomplete emptying
→ "FUNWISE"
- score out of 35 } mild (0-7), moderate (8-19), and severe (20-35)
- **IPSS includes 8th question on impact on QOL (scored 0-6)**

What ancillary tests should be performed for men with LUTS?

- mild symptoms } observation
- moderate to severe symptoms } uroflowmetry, PVR
} consider UDS and cysto but NOT ROUTINELY DONE
- patient with complications of BPH } surgical management

What are the absolute indications for surgical management of BPH? } "SHITRR"

- bladder **S**tones
 - recurrent gross **H**ematuria
 - recurrent **I**nfections
 - **T**herapy failure (meds)
 - **R**enal insufficiency
 - **R**efractory retention (failed ≥ 1 TOV)
- \ } CUA Guidelines say only these 3 are
/ absolute indications

What are the BPH Panel Guidelines regarding uroflowmetry?

- **Flow rates are valid only if voided volume is >125-150 mL**
- Flow rate is the best noninvasive test to detect LUT obstruction
→ BUT, there is no "cutoff" value that represents appropriate therapy
- Qmax more specifically identifies patients with BPH than Qave
- no age or voided volume correction for "N" Qmax, but it does decrease w/ older age & at lower volumes
- **Qmax >15cc/s appears to have worse Rx outcomes after TURP** cf patients with Qmax <15cc/s
- Qmax <15cc/s does not differentiate between obstruction & bladder decompensation
- **symptoms (subjective or quantified) do not correlate with uroflowmetry measurements**

What are the BPH Panel Guidelines regarding PVR?

- PVR has significant intra-individual variability that limits clinical use
- **PVR does not correlate well with other signs or symptoms of BPH**
- **larger PVR may predict higher failure rates with watchful waiting**
→ BUT, there is no threshold to define a poor outcome
- it is uncertain whether PVR predicts outcome of surgical management
→ should be viewed as a "safety parameter", in that those with high PVR should be monitored more closely if they choose non-surgical management
- it is uncertain whether PVR indicates impending bladder or renal damage
→ depends on compliance of bladder
- PVR can be measured accurately with transabdominal U/S

What is the role of Pressure-Flow Studies (PFS) in men with LUTS?

- differentiates low Qmax due to obstruction from that caused by decompensated or neurogenic bladder
- can also identify high-pressure obstruction in symptomatic men with normal flow rates
- **does not predict benefit from surgery any better than Qmax**
→ some patients with low-pressure, low flow may still benefit from surgery

What is the role of CMG in men with LUTS?

- filling cystometry adds little info in most men with LUTS
- may have value in patients with known or suspected neurologic lesions and LUTS
→ PFS better and give more info

What is the significance of OAB contractions in men with LUTS?

- **present in ~60% of men with LUTS**
- resolves in most after surgery } 25% still have it afterwards
→ pre-op CMG DOES NOT reliably predict who will still have OAB after surgery

What is the role of Cystourethroscopy in men with LUTS?

- **NOT RECOMMENDED to decide need for Sx** } minimal correlation b/w appearance & outcome
- does help determine the best technical approach } TURP vs TUIP vs open simple

What are the indications for Cysto in men with LUTS? }}} “CHUCS”

- suspicion of **CIS** (severe irritative symptoms)
- micro or gross **Hematuria**
- hx of **Urethral stricture** disease (or RFs such as urethral injury, urethritis)
- hx of bladder **Cancer**
- prior **Surgery** for LUTs (eg prior TURP)

What are the indications for upper tract imaging in men with LUTS? }}} “SHIRS”

- hx of **Stones**
- **Hematuria**
- **Infections** (UTIs)
- **Renal insufficiency**
- hx of urinary tract **Surgery**
→ U/S + KUB best choice if indicated
→ only 10-25% have abN findings that alter management in men WITHOUT indications

EFFECTIVENESS AND SAFETY OF MEDICAL THERAPY FOR BPH

What is BPH?

- microscopic BPH } proliferative process of the stromal & epithelial elements of the prostate
- macroscopic BPH } enlargement of the prostate from microscopic BPH
- clinical BPH } constellation of LUTS, poor bladder emptying, urinary retention, OAB, UTIs, hematuria, and renal failure (now rare)

What are the goals of medical Rx for BPH?

- relieving LUTS
- decreasing BOO
- improving bladder emptying
- relieving OAB activity
- reversing renal insufficiency
- preventing disease progression (worsening of symptoms, future gross hematuria, UTI, AUR, or the need for surgical Rx)

What are the factors often used to try to predict successful medical management of BPH?

- worse AUA symptom score
- Q max
- AUR
- OAB
- PVR
- obstruction on UDS

What outcome measures are often used to measure response to treatment of BPH?

- symptoms
- UTIs
- Qmax
- AUR
- PVR
- renal insufficiency

MEDICAL THERAPY FOR BPH

What are the options for non-surgical management of BPH?

- 1) watchful waiting
- 2) behavioral modifications
→ bladder retraining, education, habits, timed voiding, limit caffeine/EtOH, etc
- 3) α -blockers
- 4) 5ARIs
- 5) combination therapy
- 6) aromatase inhibitors
- 7) phytotherapy
- 8) TCA
- 9) anticholinergics
→ for minimal obstruction + OAB
- 10) circumvention therapy
→ CIC, indwelling Foley, S/P
- 11) investigational (eg Botox)

What are the main categories of medical therapies used for BPH?

- 1) α -blockers
- 2) 5 α -reductase inhibitors
- 3) aromatase inhibitors
- 4) plant extracts (phytotherapy)

What prompted enthusiasm for medical therapy for BPH?

- morbidity of Sx
- failure to consistently achieve successful outcome
- necessity for re-Sx
- Sx may increase risk of delayed life-threatening cardiac events

Who are the ideal candidates for medical therapy for BPH?

- bothersome symptoms
- no absolute indications for surgery (SHITRR)

What are the reasons against starting preventative medical Rx for BPH?

- manifestations of BPH not usually life-threatening
- therapy exists if BPH does become clinically evident
- cost of long term meds
- adverse events associated with long-term drug exposure

α -BLOCKERS FOR BPH

What is the classification of α -blockers for BPH (CHART)?

- 1) nonselective } phenoxybenzamine (10mg bid)
- effective but lots of S/Es
- 2) α_1 selective (short-acting) } prazosin (2mg bid)
 } alfuzosin IR (2.5mg tid)
 } indoramin (20mg bid)
- 3) α_1 selective (long-acting) } terazosin (5-10mg od) → hytrin
 } doxazosin (4-8mg od) → cardura
 } alfuzosin SR (10mg od) → xatral
- 4) **α_{1a} subtype selective** } tamsulosin (0.4mg od) → flomax

Why are selective, long-acting α -blockers preferred?

- multicentre, randomized, double-blind, placebo-controlled studies have shown efficacy & safety
 - long-acting allows daily dosing
 - less S/Es with selective α -blockers
- effectiveness of α -blockers is DOSE DEPENDENT and DURABLE

What are the contraindications to α -blocker therapy?

- known hypersensitivity to α -blocker
- upcoming cataract surgery (floppy iris syndrome)
- previous life-threatening sulfa allergy
- postural hypoTN
- hx of priapism (relative)
- pregnancy (relative)

What are the common S/Es of α -blocker therapy?

- fatigue/asthenia
- runny nose/rhinitis
- dizziness } not related to CV effect of meds but due to CNS effect (most with prazosin, then doxazosin)
- syncope/hypoTN
- headache
- GI upset
- retrograde ejaculation } incidence different with different meds (eg flomax > xatral)
- priapism

What is the $T_{1/2}$ of the different α -blockers?

- terazosin } 12hrs
- doxazosin } 22hrs
- alfuzosin } 10hrs
- tamsulosin } 9-13hrs

What is the role of α -blockers in the treatment of BPH and coexisting HTN?

- ~30% of men treated for BPH also have HTN
 - BP lowering by terazosin and doxazosin is clinically significant
- \ reasonable to Rx men with
/ BPH and HTN

	Onset	Side effects	Special considerations
Terazosin	2 weeks	1. somnolence 2. asthenia 3. postural hypotension 5% 4. syncope 1% 5. dizziness 6. nasal congestion 7. impotence 8. ↓ cholesterol 9. priapism	- 1 st dose effect at 3 hours - PM dosing, start w/ 1 mg - interaction with verapamil (Isoptin®) - Irritative sx improvement at 10 mg; obstructive sx at 5 mg; total sx at 10 mg; flow ↑ at all doses - Postural hypotension sig at 5 mg - special indication: hypertensive men
Doxazosin	1 week	1. somnolence 2. asthenia 3. hypotension > terazosin 4. syncope 0.5% 5. dizziness 6. headache 7. nausea 8. ↓ cholesterol 9. priapism (rare)	- 1 st dose effect at 2-6 hours (check BP routinely) - AM or PM dosing (?why) - Sig sx improvement at 4 and 8 mg only (vs. PFR improvement at all doses) - special indication: hypertensive men
Tamsulosin	adjust dose at 2-4 weeks ? onset	1. dizziness 3% 2. abnormal ejaculation 3% - retrograde - ↓ volume 3. headache 2%	- Fasting results in 30% ↑ in bioavailability and 40-70% ↑ in peak concentration - Postural hypoTN, syncope & tachycardia 1% for both placebo and Rx. Night time dosing & post-dose BP monitoring is not necessary - special indication: AUR, pts at risk of hypoTN, pts who don't tolerate terazosin/doxazosin at 10/8 mg

ANDROGEN SUPPRESSION FOR BPH

What is the role of 5 α -reductase in BPH?

- enzyme that converts testosterone to DHT } **DHT is the key hormone for the prostate**
- genetic deficiency results in rudimentary prostate and feminized external genitalia
- suppression of T and DHT reduces prostate volume in men with BPH
 → regression of primarily glandular epithelial elements of prostate
- type 1 and type 2 isoenzymes exist in prostate
 → type 1 exists mainly in skin and liver

What are the different classes of androgen suppression meds (CHART)?

- 1) GnRH analogs
 - Leuprolide (Lupron/Eligard)
 - goserelin (Zoladex)
- 2) Progestational Agents
 - 17 α -hydroxycortisone
 - megestrol (Megace)
- 3) anti-androgens
 - flutamide (Chimax)
 - bicalutamide (Casodex)
- 4) 5 α -reductase inhibitors
 - finasteride (Proscar) } type 2 inhibitor
 - dutasteride (Avodart) } types 1 & 2

What are the benefits of 5ARIs?

- decreases prostate volume (20-30%)
- improves symptom scores (only ~1unit)
- reduces risk of AUR
- increases Qmax (only ~2cc/s)
- decreases serum & prostatic DHT levels
- decreases PSA (50%) } makes more sensitive (even Propecia 1mg decreases PSA)
- prevents recurrent gross hematuria from BPH (finasteride)
- decreases risk of PCa (PCPT & REDUCE)

What are the side effects of 5ARIs?

- **ED (most common S/E on MTOPS, PLESS and PCPT)**
- decreased libido
- ejaculatory disorder
- breast tenderness/swelling

What are the findings of the PLESS trial?

- Proscar Long-term Efficacy and Safety Study
- multicentre, randomized, double-blind, placebo-controlled trial
- 3040 men over 4yrs
- **daily finasteride 5mg vs placebo**
- mean prostate volume was 55 cm³ (biased for larger prostates)
- **improved symptom scores, flow rates, and decreased prostate volume**
- **57% risk reduction in incidence of AUR**
- **55% risk reduction of undergoing BPH-related surgery**
 - benefits more pronounced in men with larger prostates
- **no difference in Dx of prostate cancer**

What are the main differences between finasteride & dutasteride?

- dutasteride is dual inhibitor of type 1 & type 2 5-AR } greater impact on inhibiting serum DHT levels
- dutasteride has longer T_{1/2} at 5weeks vs 6-8hrs for finasteride
- slightly faster onset of effectiveness with dutasteride

COMBINATION THERAPY FOR BPH

What were the findings of the VA Cooperative Study on BPH?

- multicentre, randomized, double-blind trial
- placebo vs finasteride vs terazosin vs combination (finasteride + terazosin)
- 1007 men followed for 1yr
- finasteride 5mg and terazosin titrated up to 10mg
 - terazosin alone better than placebo and finasteride alone } symptoms, Qmax
 - combination same as terazosin alone
 - superiority of α -blockers over 5ARIs for BPH over 1yr interval

What were the findings of the European PREDICT trial on BPH?

- Prospective European Doxazosin and Combination Therapy trial
- multicentre, randomized, double-blind, placebo-controlled study
- placebo vs doxazosin vs finasteride vs combination (finasteride + doxazosin)
- 1089 men followed for 1yr
- finasteride 5mg and doxazosin titrated up to 8mg
 - doxazosin alone better than placebo and finasteride alone } symptoms, Qmax
 - combination same as doxazosin alone
 - no benefit of 5ARI as monotherapy

What are the findings of the MTOPS trial?

- Medical Therapy Of Prostatic Symptoms (NEJM '03)
- multicentre, randomized, double-blind, placebo-controlled, prospective trial
- **3047 men** followed for 5 yrs } TRUS Bx at baseline + at 5yrs in 37% of patients
- inclusion criteria } **PSA <10, IPSS 8-30, Qmax 4-15cc/s**
- placebo vs doxazosin vs finasteride vs combination (finasteride + doxazosin)
 - finasteride 5mg and doxazosin titrated up to 8mg
- progression defined } IPSS rise of ≥4, AUR, renal failure, recurrent UTI, incontinence
- RESULTS
 - **Dual Rx reduced risk of progression significantly more than either drug alone**
 - all Rx arms improved IPSS and Qmax cf placebo
 - combination Rx arm significantly more
 - finasteride & combination Rx arms reduced risk of AUR & need for BPH Sx
 - AND reduced PSA by ~50% & prostate volume by ~20%
 - risk of recurrent UTIs & incontinence were too low to analyse
 - NO cases of renal failure due to BPH
 - most common S/E of doxazosin & combination Rx was dizziness
 - most common S/E of finasteride was ED (2nd most common S/E of dual Rx arm)
 - **NNT to prevent a case of BPH progression was 8.4 for combination therapy**
 - **if PSA >4 then the NNT was 4.7 (higher risk of progression if PSA >4)**
 - **if volume >40g then NNT was 4.0**

AROMATASE INHIBITORS FOR BPH

What is the rationale for using aromatase inhibitors for BPH?

- estrogens have inductive affect on prostatic stroma
 - prostatic stroma may play a role in BPH too (not just epithelial elements)
- estrogens increase prostatic stroma in animal models
- estrogens enhance the ability of androgens to induce BPH in dogs
- **stromal hyperplasia can be prevented by aromatase inhibitors**

PHYTOTHERAPY

What are the suggested mechanisms of action of plant extracts (CHART)?

- 1) inhibition of 5 α -reductase (types 1 & 2) } eg Saw Palmetto (*Serenoa repens*)
 - improves symptoms but does not decrease risk of AUR, need for Sx, etc
- 2) anti-inflammatory } eg flavonoids are COX inhibitors
- 3) interference of growth factors } eg Saw Palmetto & African plum (*P. africanum*)
 - anti-androgenic
 - estrogenic
 - inhibition of aromatase
 - decrease of SHBG
 - alteration of cholesterol metabolism
 - action on α -adrenergic receptors
 - free radical scavenger
 - alteration of lipid peroxidation
 - modulation of prolactin-induced prostatic growth
 - protection of bladder and detrusor function
 - placebo effect

***** NEJM 2006 – Bent et al *****

- double blind RCT
- 225 men all >49yrs old with moderate to severe LUTS
- 1yr treatment with saw palmetto (160mg BID) VS placebo
- no change in AUA symptom score, Qmax, prostate size, PVR, QOL, serum PSA

FUTURE STRATEGIES FOR MEDICAL MANAGEMENT OF BPH

What medications for BPH are being studied?

- selective endothelin antagonists } endothelin elicits potent contraction in prostate
- NO inhibitors } NO mediates smooth muscle activity
- Botox

Chapter #88 – Minimally Invasive and Endoscopic Mgt of BPH

INTRAPROSTATIC STENTS

What are the indications for intraprostatic stents?

- unfit for Sx in short & long term, where alternative is months or lifetime of urethral catheterization
- DSD
- post-brachy BOO
- urinary incontinence after RP
- anastomotic strictures
- complex or recurrent urethral strictures

What types of intraprostatic stents are used?

- 1) temporary stents } nonabsorbable
 - spiral stents eg Urospiral, Memokath, Prosta Coil
 - polyurethane stents eg intraurethral catheter, Barnes, trestle
- } biodegradable
 - polyglycolic acid
- } don't become covered by urethral epithelium nor become incorporated into urethral wall
- } 50-90% success rate
- } fairly easy but can't catheterize or cystoscope with stent in place
- } moderate complication rate
 - encrustation, migration, breakage, bacteriuria, SUI, hematuria
- } will likely have main role as adjuvant therapy after TUMT, HIFU, etc
- 2) permanent stents } metal
 - } becomes covered by urothelium (eg UroLume)
 - } fairly high complication rate
 - epithelial hyperplasia, migration of stent, irritative LUTS, painful ejaculation, encrustation

TUNA OF PROSTATE

What is TUNA of the prostate?

- **low-level RF energy (490kHz) used to produce localized necrotic lesions (1cm)**
- can be delivered under local
- doesn't work well on large blood vessels (heat dissipates)
- hot central core (90-100C) with very quick decline in temp as distance increases from needle
- NOS receptor damage occurs earliest, with damage to adrenergic receptors at 1-2 weeks

How successful is TUNA?

- almost as good as TURP wrt improvement in symptoms and Qmax
 - ~13 symptom unit improvement
 - ~6cc/sec improvement in Qmax
- **retreatment more common** after TUNA than TURP } 15% need retreatment within 2yrs
- complication rate is low

What are the indications for TUNA?

- lateral lobe enlargement
- $\leq 60\text{g}$ prostate
- poor-surgical risk patients

What are the potential complications after TUNA?

- **urinary retention (40% during first 24hrs)**
- **irritative LUTS (40%)**
- UTI
- urethral strictures (1%)
- hematuria (usually mild and short lasting)
- no adverse effect on sexual function
- no UI after TUNA

TUMT

What is TUMT of the prostate?

- **microwave heating of prostate results in thermal damage to adenoma, sympathetic nerve endings, and induction of apoptosis**
- hemorrhagic necrosis of tissue after 60 minutes of exposure to minimum 45C
- machines delivering higher power have better results

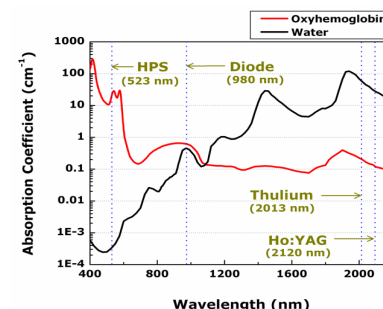
How successful is TUMT?

- moderate improvement in symptoms and Qmax
 - ~9 symptom unit improvement
 - ~3cc/sec improvement in Qmax
- prolonged catheterization more common after TUMT
- **re-treatment more common** often after TUMT cf TURP
- **lower rate of retrograde ejaculation & urethral strictures**

What are the potential complications after TUMT?

- **urinary retention } prolonged catheterization common**
- irritative LUTS
- UTI

Laser Absorption



LASERS

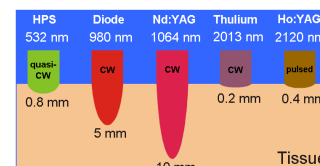
What is a laser?

- light amplification by the stimulated emission of radiation
- most of energy wasted in the form of heat
- **coagulation achieved at temps of 70-90C and vaporization at temps >100C**

What are the different types of lasers used to treat the prostate?

- 1) Neodymium:YAG } 1064nm
(Nd:YAG) } poorly absorbed by water and so leads to coagulation
} continuous energy wave
} penetrates tissue relatively deeply
- 2) Potassium Titanyl Phosphate } **532nm**
(KTP) } continuous energy wave
} **penetrates only half as deeply** as Nd:YAG
} **higher energy** than Nd:YAG
- 3) Holmium:YAG } 2100nm
(Ho:YAG) } absorbed by water and leads to vaporization
} energy emitted in a series of rapid pulses over a few milliseconds
} produces more of a cutting effect and less of a hemostatic effect
- 4) Diode } less wasted energy
} smaller and more portable because don't need large cooling devices

Optical Penetration Depth



What are the methods of laser energy delivery?

- side firing } metal/glass reflector, prismatic internal reflector
- end firing } bare tip, sculptured tip, sapphire tip
- interstitial } bare tip, diffuser tip, diffuser tip with temp transducer

Which procedures use laser on the prostate?

- Transurethral Ultrasound-guided Laser-induced Prostatectomy (TULIP)
→ side-firing laser
- Visualized Laser Ablation of the Prostate (VLAP)
- end-firing/contact laser
- TransUrethral Evaporization of the Prostate (TUEP)
- interstitial
- Holmium Laser Enucleation of the Prostate (HoLEP) } acts on water
- **Photoselective Vaporization of the Prostate (Greenlight KTP PVP) } acts on HgB**

What are the advantages & disadvantages of laser therapy?

advantages	disadvantages
<ul style="list-style-type: none"> - no bleeding - can treat anticoagulated patients - no TUR syndrome - less irrigation use 	<ul style="list-style-type: none"> - no tissue for pathology - longer catheterization times with coagulation necrosis - prolonged irritative symptoms - expensive

What are the potential complications of laser therapy of the prostate?

- **urinary retention } prolonged catheterization common**
- bacteriuria
- urethral strictures

TURP

What are the indications for a TURP?

- SHITRR (absolute indications = TRR as per CUA Guidelines)
- most common reason for TURP is symptoms (relative indication)

What is the IPSS ?

- AUA Symptom Score + global bother score
 - AUA symptoms score = 7 questions
 - frequency, urgency, nocturia, weak stream, intermittency, straining, emptying (FUNWISE)
 - mild (score 0-7), moderate (score 8-19), severe (score 20-35)
 - global bother score (0-6)

What is the BPH Impact Index?

- developed to determine impact of BPH
- 4 questions } urinary discomfort, worry about health, urinary bother, affect on lifestyle

What is the recommended work-up prior to a TURP?

- urinalysis } r/o infection
- DRE } r/o cancer and also estimate size of gland
- serum creatinine
- OPTIONAL } uroflowmetry, pressure-flow studies
- NOT ROUTINELY RECOMMENDED } filling CMG, cystoscopy, upper tract imaging

What are the indications for upper tract imaging prior to a TURP? } } SHIRS

- hx of GU tract **S**urgery
- **H**ematuria
- hx of **I**nfections (UTI)
- **R**enal insufficiency
- hx of **S**tones

What are the recommendations on pre-TURP ABx?

- prophylactic ABx } 1st generation cephalosporin + gentamicin
- po ABx until after catheter removed

How successful is a TURP?

- reduction of symptoms by ~85%
- ~90% of patients satisfied at 5yrs after TURP

What are the potential complications of a TURP?

- | | |
|------------------|-------------------------------|
| → peri-op (~15%) | → late post-op (8%) |
| - retention | - delayed bleeding |
| - UTI/sepsis | - BN contracture |
| - bleeding | - urethral strictures |
| - clot retention | - meatal stenosis |
| - injury to UO | - urinary incontinence (rare) |
| - rectal injury | - ED (rare) |
| - TUR syndrome | |

What is the management of extravasation & perforation of the prostatic capsule?

- occurs in 2% } restlessness, N/V, abdo pain, abdo distension
- control any bleeding & stop procedure immediately
- urethral catheter drainage (enough in 90%)
- S/P tube if extensive extravasation and/or concern about infecting perivesical tissue

How does TUR syndrome present?

- occurs in 2%
- **usually not symptomatic until serum Na \leq 125 mEq/dL**
 - N/V
 - HTN
 - bradycardia
 - pulmonary edema
 - confusion
 - visual disturbances
 - H/A
 - seizures

What are the RFs for TUR syndrome?

- gland size >45g
- long resection time >90 mins
- deep resection/capsular perforation
- open veins
- lots of irrigant use
- elevated height of irrigant during TURP
- CHF
- liver failure

What is the management of TUR syndrome?

- ~20cc/min of irrigant fluid absorbed during TUR
- **likely dilutional hyponatremia**
- glycine metabolized to glycolic acid and ammonium } **ammonium toxicity may play a role**
- Rx → depends on serum Na and patient condition } can range from confused to comatose
 - stop TURP as soon as hemostasis achieved
 - 3 way Foley to CBI with NS
 - ABCs } 100% O₂, VSq2h (+/- neurovitals)
 - may need intubation if ↓'d LOC or evidence of elevated ICP
 - lab investigations } CBC, lytes, creat, Ca, Mg, PO₄ in PACU and then lytes q4h
 - manage fluid overload } lasix 40 mg iv or mannitol 0.5 g/kg iv
 - consider hyperventilation if signs of elevated ICP
 - manage hyponatremia } 200cc of hypertonic 3% NS iv over 1-2h (if N renal function, HD otherwise)
 - don't over correct Na
 - 1 mmol/L/hr up to 20 mmol/L in 48hrs
 - if having seizures, correct at 8-10 mmol/L/hr
 - benzo's for seizures } lorazepam 4-8mg iv
 - } dilantin 20mg/kg iv

What is the management of intra-op priapism?

- phenylephrine or ephedrine injected into corpora cavernosa } if unsuccessful, may need PU
- deepen anesthetic
- ketamine
- dorsal nerve block anesthetic

What are the indications for PU to do a TURP?

- tight urethra that doesn't accept resectoscope
- long phallus
- previous urethral reconstruction
- persistent erection
- penile implant

What are the advantages of bipolar TURP?

- less bleeding
- earlier removal of catheter
- earlier discharge from hospital

What is the etiology of hemorrhage post TURP?

- 1) Arterial bleeding
- 2) Venous bleeding } Capsular perforation
- 3) Coagulopathy } primary (ATIII deficiency, low platelets, uremia, etc.)
 } medication related (coumadin, heparin, ASA)
 } secondary (from TUR syndrome)

How does one deal with severe bleeding from TURP?

→ Intraoperative

- 1) General measures
 - ABCs } if hypotensive, bolus with crystalloid/NS or colloids/albumin
 - X&T, stat CBC & coags
 - 2 large bore IVs
- 2) Local measures
 - Arterial } fulguration
 - Venous } fulguration
 - insert catheter, blow up balloon & tamponade
 → Foley to traction x 10 minutes + irrigate → if venous bleeding, colour should improve
- 3) Systemic
 - correct any coagulopathy
 - transfuse: pRBC, cryo, platelets, FFP

→ Postoperative

- 1) General measures
 - ABCs } if hypotensive, bolus with crystalloid/NS or colloids/albumin
 - X&T, stat CBC/coags
 - 2 large bore IVs
 - correct coagulopathy if present
- 2) Immediate bleeding in PACU = faulty intraoperative hemostasis
 - manual catheter irrigation to declot, then high-flow CBI
 - full balloon (50cc) on traction
 - double balloon catheter
 - iced saline irrigation
 - alum and/or silver nitrate and/or formaldehyde irrigation
 - Amicar (intravesically or systemically) } NO LONGER available
- 3) Return to OR if fails
 - 2nd look to declot, coagulate and rollerball
 - open attempt at hemostasis if failed transurethral mgt
 - suture ligation at BN
 - Malament stitches } nylon purse-string at BN, bring out through ant abdo wall and remove 1-2d later
 - O'Connor stitches } plicate posterior prostatic capsule with O-chromic
 - pack prostatic fossa
 - place SP tube
 - ligate internal iliacs
 - radiologic embolization of bleeder
- 4) Systemic Measures
 - amicar 5 g IV loading dose over 1 hr then 1 g/hr x 8 hr (up to 30 g/24 hr) } NOT AVAILABLE
 - correct systemic coagulopathy: cryo, platelets, FFP, vitamin K, protamine
- 5) Delayed bleeding = sloughing of tissue rendered ischemic during initial procedure
 - ensure pt stable
 - irrigate bladder + CBI
 - r/o other causes of hematuria (H&P, labs, etc) } treat other causes if found
 - correct systemic coagulopathy
 - if bleeding from prostate: traction on Foley, Amicar, cystoscopy + fulguration

TUIP

What is a TUIP?

- **incision using Collings knife made at 5- and 7-o'clock**
- **incision from just distal to UO to just proximal to verumontanum**
- incisional depth down to filaments of external capsule

What are the indications for a TUIP?

- small prostate with BOO (usually <30g) } high BN
- usually younger man

How successful is a TUIP?

- improved symptoms and Qmax } not as good as TURP
- shorter OR time and shorter duration of catheterization
- similar re-operation rates
- lower rates of retrograde ejaculation and ED (try to avoid if fertility still an issue)

TRANSURETHRAL VAPORIZATION OF PROSTATE

What is TUVF?

- combines vaporization and desiccation
 - vaporization steams tissue away using high heat
 - desiccation uses lower heat to dry out tissue
- use of rollerball on vapor-trode setting

How successful is TUVF?

- comparable improvements in symptoms score and Qmax
- some similar complications as TURP
 - irritative LUTS
 - UTI
 - 1yr re-operation rate
 - urethral strictures
- better than TURP
 - earlier removal of catheter
 - **less hematuria and transfusion rate**
 - lower retrograde ejaculation rate
 - shorter hospital stay
- worse than TURP
 - longer OR time
 - higher post-op retention rates
 - **higher rates of ED**
 - **higher rates of incontinence**

OTHER TECHNOLOGIES

What other therapies are used to treat LUTS?

- water-induced thermotherapy } low complications but high rate of retreatment
- transurethral ethanol ablation of the prostate } low complication rate
- roto-resection of the prostate } low complication rate

Chapter #89 – Open Prostatectomy

INDICATIONS FOR OPEN PROSTATECTOMY

What are the indications for open prostatectomy? } } } “75 LUSH Treatment”

- SHITRR } Stones, Hematuria, Infections, Treatment (meds) refractory, Renal Insufficiency, Retention
- gland >75g
- Lithotomy not possible (hips, etc)
- Urethral conditions (complex or recurrent strictures, etc)
- Stone (bladder) too large for transurethral fragmentation
- Hernia (inguinal) requiring concomitant repair
- Tic requiring concomitant diverticulectomy

What are the contraindications to open prostatectomy?

- small fibrous gland
- presence of prostate cancer
- previous complex pelvic surgery that limits access to the prostate gland

What are the different forms of open prostatectomy?

- 1) retropubic } enucleation via a direct anterior incision in the prostatic capsule
 } aka **Millin procedure**
- 2) suprapubic } enucleation via an incision in lower anterior bladder wall
 } aka transvesical prostatectomy

What are the advantages of the different open prostatectomy methods?

→ retropubic

- 1) **excellent anatomic exposure**
- 2) direct visualization of adenoma to ensure complete removal
- 3) precise transection of apex and urethra distally to preserve continence
- 4) clear visualization of prostatic fossa to control bleeding
- 5) **minimal to no trauma to the bladder**

→ suprapubic

- 1) direct access to bladder } **good if concomitant stone or tic in bladder**
- 2) **allows access to large intravesical median lobe**
- 3) preferred in obese men in whom it is hard to gain access to prostatic capsule

What are the advantages of open prostatectomy over TURP?

→ **overall better than any other treatment wrt symptoms and Qmax**

- lower retreatment rate
- more complete removal of adenoma
- avoids risk of TUR syndrome

What are the disadvantages of open prostatectomy vs TURP?

- need for lower midline incision
- longer hospitalization
- increased potential for peri-op hemorrhage

PRE-OP EVALUATION & OPERATING DAY PREPARATION

What is involved in the pre-op work-up prior to an open prostatectomy?

- Hx + IPSS
- Physical including DRE + PSA (**r/o PCa**)
- CBC, lytes, creatinine, PTT/INR, cross & type for 2units pRBCs
- urinalysis +/- urine C&S
- uroflowmetry
- CXR, EKG
- OPTIONAL } cystoscopy or TRUS
 - to evaluate size of gland
- } upper tract imaging
 - known renal disease, abN renal function, recurrent UTIs, hematuria

What is the pre-op prep required before a TURP?

- NPO after MN
- Fleet enema morning of surgery
- peri-op dose of Ancef or Ampicillin

SURGICAL TECHNIQUE

Describe the initial steps of an open prostatectomy?

- separate rectus muscles, incise transversalis fascia and expose space of Retzius
- de-fat periprostatic adipose tissue to expose superficial branch of the DVC
- open endopelvic fascia bilaterally
- transect puboprostatic ligaments bilaterally
- need venous & arterial control } ligate DVC with 3-0 suture at apex
 - } ligate superficial branch of dorsal vein at bladder
 - } secure lateral pedicles by placing figure-of-eight stitch deep into prostatovesical jxn at level where SVs insert laterally to control arterial supply to prostate

Describe the main steps of a RETROPUBIC open prostatectomy (Millin).

- transverse capsulotomy made over anterior aspect of prostate 1.5-2.0cm distal to the BN
 - transverse incision prevents extending incision down into EUS
- use Metzenbaum scissors to dissect overlying prostatic capsule from the underlying prostatic adenoma
- finger dissect adenoma from capsule laterally and posteriorly
- incise anterior commissure from BN to apex, separating lateral lobes anteriorly, and exposing posterior prostatic urethra
- insert finger to level of verumontanum and fracture urethral mucosa
 - be careful not to injure EUS
- sharply divide urethra at apex to separate and remove first the left then the right lateral lobes
- incise mucosa and remove median lobe if present
- strip of posterior prostatic urethra preserved
- remove any remaining adenoma in prostatic fossa and obtain hemostasis
 - for persistent bleeding, place 4-0 suture in the BN at 5 and 7 o'clock
 - be careful not to incorporate UO
- if BN looks obstructive, make wedge resection at 6 o'clock & advance bladder mucosa into prostatic fossa
 - helps prevent BN contracture
- insert 22Fr 3-way Foley into bladder with 50cc in balloon
- close prostatic capsule with 2-0 chromic suture
- irrigate bladder
- place JP drain

Describe the main steps of a SUPRAPUBIC open prostatectomy.

- fill bladder with 250cc and clamp off catheter
- 3-0 vicryl stay sutures placed in anterior wall of bladder
- vertical cystotomy made down to within 1cm of BN
 - 3-0 vicryl figure-of-eight suture placed at most caudal end of cystotomy to prevent migration of cystotomy during enucleation
 - alternatively a transverse incision can be made
- incision in mucosa of BN distal to trigone
- develop plane posteriorly between adenoma and prostatic capsule at 6 o'clock position
- dissect adenoma circumferentially and inferiorly down to apex using blunt dissection
- transect prostatic urethra and avoid excess traction so as not to injure EUS
- inspect prostatic fossa for residual adenoma and obtain hemostasis
 - can advance bladder mucosa into prostatic fossa at 5 and 7 o'clock positions at the prostatovesical junction to control main arterial blood supply to prostate
 - if continues, can place purse string #2 nylon suture around BN and bring out through skin to tamponade prostatic fossa (**Malament maneuver**); remove on POD 1 or 2
- insert 22Fr 3-way Foley with 50cc in balloon
- place 24Fr Malecot S/P tube at dome of bladder
- cystotomy closed in 2 layers with 2-0 (internal) and 3-0 (external) vicryl sutures
- irrigate bladder
- place JP drain

POST-OP MANAGEMENT

What is the post-op management after open prostatectomy?

- monitoring of JP, S/P tube, and 3way catheter
- serial CBC
- traction for significant bleeding } if excessive, can perform cysto + fulguration
 - } re-exploration if marked hemorrhage persists
- remove CBI once clear
- D/C catheter on POD #2
- clamp S/P tube once catheter removed
- D/C JP on POD #3 if <75cc/od
- S/P removed on POD #5 once voiding well

COMPLICATIONS

What are the potential complications of open prostatectomy?

- overall rate of M&M is very low
- urinary incontinence } rare
- urgency & urgency incontinence } usually self limited (several weeks to months)
- ED } 3-5% (more common in older men)
- retrograde ejaculation } occurs in 80-90%
- UTI
- acute epididymitis
- BN contracture } 2-5% (occurs 6-12 weeks after surgery)
 - } initial mgt is dilation or TUIBN
- urethral stricture
- **hemorrhage requiring blood transfusion } 5-10% risk**
- DVT/PE/MI/CVA } <1%

RISK FACTORS

What are the potential RFs for the development of PCa? } } } “SO FAR Prostate Disease Free”

- 1) **Smoking** } may be associated with more advanced stage PCa
- 2) **Obesity** } elevated BMI associated with increased risk of PCa
 - increased oxidative stress
 - } some studies suggest associated with decreased risk of PCa
 - likely because obesity associated with decreased androgen levels (as such lower PSA levels), which biases against TRUS Bx
- 3) **Family Hx** } RR increases based on # of family members, degree of relatedness, and age at which they were affected
 - ≥10 candidate PCa genes reported
- 4) **Age**
- 5) **Race** } blacks at increased risk while asians at decreased risk
 - may be due to increased androgen exposure
- 6) **Prostatitis or hx of STD's** } chronic inflammation leads to cellular hyperproliferation, which increases risk of PCa
 - (proliferative inflammatory atrophy)
 - defects in cellular defense against infection & oxidative stress
- 7) **Drinking EtOH** } red wine may have a protective effect (antioxidant)
 - } likely no increased risk for light to moderate drinkers
- 8) **Fatty diet** } associated with an increased risk of PCa, especially for polyunsaturated fats
 - may actually be effect of low vegetable (antioxidants) intake
 - ?cadmium exposure

How does sexual activity & vasectomy affect risk of PCa?

- sexual activity } frequent ejaculations may protect against PCa (CONTROVERSIAL)
- vasectomy } may be associated with very slightly higher risk of PCa (CONTROVERSIAL)
 - } likely an ascertainment bias (more likely to see urologist later on)

Table 90-2 -- Family History and Risk of Prostate Cancer

Family History	Relative Risk	Absolute Risk (%)
None	1	8
Father or brother	2	15
Father or brother affected < 60 years	3	20
Father and brother	4	30
Hereditary prostate cancer	5	35-45

What is the definition of Hereditary PCa?

- 1) ≥3 affected family members
 - 2) PCa in 3 consecutive generations
 - 3) 2 affected family members both before age 55
- relatives of PCa patients <55yrs are at much higher risk for PCa
- there is a stronger familial clustering in families with early-onset PCa
- **# of affected family members & their age at Dx** are the most important determinants of risk among relatives
- \ - accounts for ~45% of early-onset PCa
} but only 9% of all PCa
/

What molecular compounds are associated with PCa risk?

- 1) androgen levels/exposure } **long-term absence of exposure to androgens is protective against the development of PCa**
 - dose-response relationship NOT established
 - } shortened CAG repeat length in exon 1 is associated with increased risk of PCa, as well as advanced HRPc
 - } abN SRD5A2 gene makes 5 α -reductase enzyme 5-fold more active, which is associated with poor prognosis
 - } genes involved in biosynthesis of testosterone have also been implicated in PCa
- 2) estrogens } **may protect against PCa by inhibiting prostate epithelial cell growth**
- 3) IGF } **high IGF levels may be associated with increased risk of PCa**
- 4) leptin } **elevated leptin levels may be associated with increased risk of PCa**
 - } may induce VEGF- and FGF-related stimulation of cell migration
- 5) Vit D } **may be associated with reduction in risk of PCa**

Why is there interest in Vitamin D and PCa?

→ low Vit D associated with PCa

- men in northern latitudes w/ less sun-derived UV exposure have higher PCa mortality rates
- PCa occurs more frequently in older men, in whom vitamin D deficiency is more common
- Blacks, whose skin melanin blocks UV radiation and inhibits activation of vitamin D, have the highest incidence & mortality rates for PCa
- diets high in dairy, which is rich in Ca (resulting in depressed levels of vitamin D), are associated with higher risk of PCa
- men in Japan, whose diet is rich in vitamin D (high fish intake), have a low incidence of PCa

What are the 10 major PCa susceptibility genes reported?

→ most well known gene overall

1) HPC1/RNaseL → 1q24-25

→ rare AD gene with high penetrance

→ abN gene results in susceptibility to viral infections & deficient apoptosis

→ R462Q nucleotide polymorphism is associated with increased PCa risk

→ DNA repair genes

2) OGG1 → 3p26

3) BRCA → 13q12

4) CHEK2 → 22q12

→ inflammatory mediator genes

5) PON1 → 7q21 } also antioxidant & free radical scavenger

6) SR-A/MSR1 → 8p22-23 } also predisposes to infections

7) MIC1 → 19p13

→ other genes

8) PCaP → 1q42

9) CAPB → 1p36

10) ELAC2/HPC2 → 17p11

ETIOLOGY AND MOLECULAR GENETICS

What is the difference between latent & clinical PCa?

- histologic (or latent) PCa is form found in ~30% of men >50yrs and 70% of men >80yrs
→ similar prevalence worldwide among all ethnicities
- clinical PCa is the form that affects 1 in 6 men in N America
→ incidence varies dramatically between and within different countries
- progression from latent to clinically evident cancer is likely a biologic continuum with overlap in the associated molecular events

What are the main tenets of the contemporary model of PCa progression?

- 1) genetic predisposition, oxidative damage, and inflammatory changes are associated with earliest steps of PCa development
- 2) downregulation of caretaker genes (eg GSTP1) by aberrant promoter methylation may increase potential for neoplastic transformation
- 3) chromosomal loss and telomere shortening may also contribute to genetic instability and progression to invasive disease
- 4) further methylation changes, loss of tumour suppressor gene function, and other mutational events are associated with mets and androgen independence

What is the role of DHT in PCa development?

- testosterone irreversibly catalyzed to DHT by 5 α -reductase
- DHT binds to intracytoplasmic ARs with much greater affinity than testosterone
- DHT binding to the AR enhances translocation of the steroid-receptor complex into the nucleus, resulting in activation of androgen response elements
- type 2 isoenzyme of 5 α -reductase is expressed predominantly in the prostate (stromal)
→ type 1 is mainly in skin & liver
- 5 α -reductase deficiency results in insufficient exposure of prostate to DHT
→ protective against development of PCa
- lack of testosterone also protects against the development of PCa
- asian men have the lowest DHT-to-testosterone ratio whereas blacks have the highest ratio

What epigenetic mechanisms affecting gene expression are implicated with the development of PCa?

- HYPERmethylation of genes
 - **DNA repair genes (GSTP1, MGMT)**
 - hormonal response genes (AR, ESR1, ESR2, RARB, RARRES)
 - genes controlling cell cycle (CCND2, CDKN2A)
 - tumour cell invasion or tumour architecture genes (APC, CAV1, CD44, CDH1, CDH13, LAMA3, LAMB3, LAMC2)
 - signal transduction genes (DAB2IP, DAPK1, EDNRB, RASSF1)
 - inflammatory response genes (PTGS2)
- HYPOmethylation of genes (CAGE, HPSE, PLAU)
- histone hypo-acetylation (CAR, CPA3, RARB, vitamin D receptor)
- histone methylation (**GSTP1, PSA**)

What is the role of COX-2 enzyme in PCa?

- PGs are inflammatory cells designed to eradicate infectious micro-organisms
→ BUT they also have potential to cause oxidative DNA damage
- COX-2 is an inducible enzyme that mediates acute & chronic inflammation, pain, and cellular repair mechanisms
→ **PCa expresses more COX-2 than benign prostatic epithelium**
- **NSAIDs, which inhibit COX-2, have been reported to be protective against PCa**

What somatic mutations are implicated in PCa?

→ OVEREXPRESSION ASSOCIATED WITH PCa

- AR } **androgen receptor mutations present in ~50% of PCa cases**
 - } amplification of AR mRNA found in HRPC, making “androgen-resistant” cells very sensitive to tiny amounts of androgen
 - explains tumour progression despite castrate serum levels
 - may also explain paradoxical PSA decline after anti-androgen withdrawal
- classic oncogenes } RB1, p53, MYC, ERBB2, and BCL2
 - } **proto-oncogene mutations found in advanced, metastatic, & HRPC**
- telomerase } reverse transcriptase enzyme that maintains or increases telomere length
 - } **↑’d telomerase expression & paradoxical shortening of telomere length seen in PIN and PCa**
- VEGF } **increased expression may correlate with clinically aggressive PCa**
- PSM antigen } transmembrane glycoprotein expressed by PCa epithelium
 - } **overexpression seen after androgen withdrawal & in HRPC**
- Epidermal Growth Factor and EGF receptor } PCa produces EGF and expresses EGFR
 - } **levels of EGFR are higher in PCa than in benign tissue**
- α-Methylacyl-CoA Racemase } **AMACR overexpression associated w/ higher risk of PCa progression**
- EZH2 } enzyme with increasingly elevated levels during PCa progression
 - } **elevated levels predict likelihood of biochemical failure after RP**

→ LOSS OF EXPRESSION ASSOCIATED WITH PCa

- NKX3-1 } androgen-regulated & prostate-specific gene on chromosome 8p21
 - } loss of either one or both alleles becomes increasingly common in prostate lesions as they progress from PIN to local, metastatic, and HRPC
- PTEN } tumour suppressor gene on chromosome 10q23
 - } loss of PTEN results in increased phosphorylation of Akt, downregulation of apoptosis, and increased cellular proliferation
 - } **loss of PTEN associated with PIN, high Gleason score, and advanced stage**
- glutathione S-transferase } protective enzyme that inactivates reactive oxygen species
 - } **no GSTP1 enzyme found in ~70% of PIN & most cases of PCa**
- p27 } cyclin-dependent kinase inhibitor that regulates progression of cell cycle (G1 to S)
 - } loss of p27 may accelerate tumorigenesis
 - } **loss of p27 expression associated w/ PCa mets & higher biochemical failure rate**
- E-cadherin } cadherin dysfunction results in loss of adhesion & is involved in cancer invasion and progression
 - } **↓’d E-cadherin expression in PCa, especially high-grade PCa**

CHEMOPREVENTION

What is chemoprevention?

- the use of natural or synthetic agents that reverse, inhibit, or prevent the development of PCa
- goal is to decrease incidence of PCa, reduce Rx-related side effects, & decrease mortality
- effective chemoprevention requires the use of non-toxic agents that inhibit specific molecular steps in the carcinogenic pathway

What are the different prevention levels?

- 1° prevention } avoid the development of disease (eg finasteride, wt loss, lycopenes, etc)
- 2° prevention } early detection of disease & prevention of progression (eg PSA, etc)
- 3° prevention } reducing M&M associated with existing disease (eg Zometa, etc)

Why is PCa an appropriate disease for primary prevention?

- 1) incidence, prevalence, and disease-related mortality
 - most common male cancer
 - significant morbidity associated with RP, EBRT, hormones
- 2) prevalence of PIN & ASAP is similar between populations at much different risks for development of clinical PCa
 - long latency between premalignant lesions and clinically evident PCa
 - suggests external environmental influences are important and potentially modifiable

What are the advantages & disadvantages of 1° prevention studies aimed at different PCa risk groups?

	ADVANTAGES	DISADVANTAGES
LOW RISK ie general population	<ul style="list-style-type: none"> - easily definable - readily available - result widely applicable 	<ul style="list-style-type: none"> - rate of progression slow - need large study population & long f/u - expensive
INTERMEDIATE RISK eg blacks family hx HPC1 linked	<ul style="list-style-type: none"> - higher risk groups - may be genetically homogeneous (HPC1-linked) 	<ul style="list-style-type: none"> - can be difficult to define - ascertainment bias - likely to be genetically heterogeneous (FmHx) - identification is invasive & expensive (HPC1-linked) - affected pts rare (HPC1-linked)
HIGH RISK ie high grade PIN or ASAP	<ul style="list-style-type: none"> - highest known risk 	<ul style="list-style-type: none"> - sampling error - diagnosis subjective - uncommon

What are the advantages & disadvantages of different 2° prevention models?

	ADVANTAGES	DISADVANTAGES
Pre-surgical	<ul style="list-style-type: none"> - early-stage disease - readily available study population - pre-Rx & post-Rx tissue available for study 	<ul style="list-style-type: none"> - short treatment period
Elevated PSA but normal Bx	<ul style="list-style-type: none"> - well-defined histologic endpoint 	<ul style="list-style-type: none"> - risk of progression undefined - sampling error
Adverse pathology after RP	<ul style="list-style-type: none"> - high risk of progression 	<ul style="list-style-type: none"> - more advanced disease - clinical endpoint
Rising PSA after RP or radiation	<ul style="list-style-type: none"> - high risk of progression 	<ul style="list-style-type: none"> - most advanced disease - clinical endpoint

Prostate Cancer Prevention Trial (NEJM '04)

What was the impetus of the PCPT?

- 1) androgens required for the development of PCa
- 2) men with congenital deficiency in 5α -reductase type 2 DON'T get BPH or PCa

What was the study design of the PCPT?

- ~19,000 men randomized } all >55yrs old (recruited '94-'97)
- normal DRE + PSA ≤ 3 ng/mL to start } PSA later adjusted for 5ARI effect (x2.3)
- randomized to finasteride (5mg/day) vs placebo for 7yrs } f/u q3/12 with annual DRE + PSA
- for-cause Bx (abN DRE or PSA >4) or end-of-study Bx } most for-cause Bx's done earlier
- primary endpoint was prevalence of PCa during 7yrs of study

What were the main findings of the PCPT?

- study stopped 15 months early
- 1) PCa prevalence reduced by 24.8% in finasteride arm } 24.4% to 18.4% (ARR of 6%)
 - 24% incidence of PCa in placebo arm is high
 - 6.6% w/ PSA <0.5
 - 27% w/ PSA 3.1-4.0
 - reduction seen in both for-cause Bx & end-of-study Bx
 - incidence of PCa in for-cause group was 7.2%
 - end-of-study Bx in men with N DRE & PSA <4ng/mL had PCa was 15%
 - largest effect seen on Gleason 6 tumours
 - 98% of tumours were clinically localized
- 2) prevalence of Gleason 8-10 tumours was ~25% higher in finasteride group } 6.4% vs 5.1% (ARR 1.3%)
 - same # Gleason 7 tumours
 - same # of deaths due to PCa in each arm
- 3) risk reductions associated with finasteride seen in all subgroups
 - regardless of age, family hx, race, and PSA level
- 4) sexual S/Es more common w/ finasteride, urinary symptoms more common in placebo arm
 - prostates in finasteride arm were 25% smaller

What are the 2 main areas of continued debate regarding the PCPT?

- 1) were the Gleason 6 cancers that were "prevented" really biologically significant?
 - 95% of men choose definitive treatment for Gleason 6 PCa
 - so in context of "clinical relevance", preventing Gleason 6 tumours decreases anxiety, cost, and morbidity associated with their treatment
 - BUT, this may not be a 'prevention' effect; rather a treatment effect as finasteride is a form of anti-androgen therapy
- 2) is increase in prevalence of higher grade tumours real or artifactual?
 - histologic artifact of anti-androgenic agent on prostatic epithelium
 - volume effect } more likely to hit small amounts of high grade PCa in smaller glands in finasteride arm (both arms got same # of biopsies)
 - if truly causing high grade PCa, there should have been more in the end-of-study Bx group
 - BUT it could be real effect } what is effect of higher T (due to decreased DHT levels) on PCa

What are the benefits & costs of finasteride use to prevent PCa?

- benefits } 6.4% overall reduction in PCa prevalence (~25% relative risk reduction)
 - } fewer urinary symptoms, lower risk of AUR, & lower need for surgical intervention
 - } avoids "burden of care" with decrease in PCa incidence by 25%
 - } 5x more likely to have PCa prevented than to have high-grade tumour
 - no decrease in mortality rates
- costs } 1.3% increase in high-grade PCa } potential need for more aggressive therapy
 - } potential excess mortality
 - } sexual side effects & cost of treatment for these side effects
 - } cost of finasteride

What are the explanations to debunk the higher incidence of high-grade PCa in the PCPT?

- decreased volume } more likely to find PCa
→ may even mean ↓ in PCa by ~25% is an underestimation
- histologic artifact of finasteride
- PSA more sensitive on finasteride } triggers more for-cause Bx
- “fudge-factor” for PSA adjustment } 2.3x used
 } may trigger more for-cause Bx
- most of PCa detected in finasteride arm was in the 1st yr
→ rate of high-grade PCa didn’t continue to ↑ over time, as would be expected if true “effect”

Who should take finasteride for prevention of PCa?

- 1) patient with +ve family history
- 2) patient worried about PCa
- 3) motivated patient (lifelong therapy)
- 4) patient with BOO from BPH

What are the main PCa chemoprevention agents studied?

- 1) Selenium } essential trace element
 - found mainly in grains, fish, meat, poultry, eggs, and dairy products
 - } marked geographic variability related to soil content
 - } important antioxidant constituent that stimulates apoptosis & decreases cell proliferation
 - } case-control and RCTs have shown that it can decrease the risk of PCA

➔ Nutritional Prevention of Cancer Trial

- RCT with 1312 patients
- oral selenized yeast vs placebo for non-melanoma skin cancer
- mean f/u of 4.5yrs
- PCa reduced bc 2/3 in selenium arm cf placebo arm
- effect strongest for PSA <4ng/mL & men w/ low starting selenium levels

- 2) Vit E } essential, fat-soluble vitamin
- } antioxidant that induces cell cycle arrest & direct anti-androgen activity
- } β -tocopherol is most active form of Vit E
- } α -tocopherol may influence PCa development

➔ **Alpha-Tocopherol, Beta-Carotene cancer prevention Trial (ATBC)**

- double-blind RCT with ~30K male smokers between 50 and 69yrs of age
- α -tocopherol (50mg/day) and β -carotene (20mg/day) alone or in combination
- primary endpoint was lung cancer incidence and mortality
- 32% reduction in PCa incidence and 41% lower mortality in α -tocopherol arm

➔ **SELenium and vitamin E Cancer prevention Trial (SELECT)**

- double-blind, population-based RCT with 32K men (Klein et al)
- normal DRE, PSA <4ng/mL, age >50 (blacks) or >55 (whites)
- selenium (200µg), vitamin E (400mg), both, or placebo only
- primary endpoint is incidence of PCa } for-cause Bx at discretion of local MDs

→ study now closed due to lack of benefit } ? ↑'d PCa due to Vit E
} ? ↑'d DM due to selenium

- 3) Soy } legume that is a high source of **isoflavones (weak estrogenic activity)**
 } inhibits benign & malignant prostatic epithelial cell growth and downregulates
 androgen-regulated genes

- 4) Lycopenes } carotenoid found mainly in cooked tomatoes & other red fruits & vegetables
 } **carotenoids have potent antioxidant activity**
 } inhibits benign & malignant prostatic epithelial cell growth
 } 2 non-placebo-controlled prospective trials showed lycopenes are active against PCa

- 5) green tea } contains **polyphenol EGCG**, which induces apoptosis & cell growth inhibition
 } low incidence of PCa among Asians, who have high dietary intake of green tea

- 6) Cox-2 inhibitors (NSAIDs)
- 7) Selective estrogen receptor modulators (SERMs)

What is the REDUCE trial?

- REduction by DUtasteride of prostate Cancer Events
 - 8200 men (between 50-75yrs old) with PSA between 2.5-10ng/mL
 - one prior normal Bx
 - dutasteride (0.5 mg od) vs placebo
 - study-mandated Bx at 2 and 4 yrs
- primary endpoint is prevalence of cancer on Bx at 2 and 4 yrs

***** results show RR reduction of 22.5% (12% to 9%) ... no ↑'d incidence of high-grade PCa *****
→ AUA Chicago '09

What are the different patterns of PIN?

- **tufting (97%)**
- micropapillary
- cribriform
- flat

What is the management of high-grade PIN found on Bx?

→ **incidence on Bx is 5-10%**

→ **risk of PCa on repeat Bx is ~25% (ranges from 16% to 45%) } cf initially N Bx = ~20%**

- PSA level, DRE, and TRUS findings not predictive of PCa on repeat Bx
- Rx → if HGPIN found on extended core Bx (12 cores), then no need to repeat Bx within 1st yr
- **CONTROVERSIAL** } role of repeat Bx several years after diagnosis of HGPIN
- if HGPIN found in TUR specimen, TRUS Bx recommended (especially for younger men)

ADENOCARCINOMA

Where is PCa most commonly located?

- majority of tumours found in peripheral zone } rest are in TZ
- **multifocal in 85% of cases** } secondary tumours are often small, low grade

What is the significance of perineural invasion?

- **perineural invasion on RP specimen does not worsen prognosis**
 - merely represents extension of tumour along plane of decreased resistance
 - others believe it MAY PREDICT T3 disease, LN +ve disease, and progression
- **perineural invasion on TRUS Bx specimen DOES predict T3 disease in RP specimen**
 - **may even predict for LN + disease**
- LVI increases risk of recurrence after RP
- extra-prostatic extension occurs preferentially posteriorly and posterolaterally

What is the route of SV involvement in PCa?

→ **25% with SV invasion on RadP are biochemically progression-free at 10yrs**

- 1) tumour penetrates out of prostate at base of gland, then grows and extends into peri-SV soft tissue, eventually into SV (most common)
- 2) direct extension through ejaculatory ducts into SV (less common)
- 3) there may be discrete mets to the SV (rare)

What are the most common sites of PCa mets?

- LNs
- bone
- lung
- bladder
- liver
- adrenal

What is the significance of PCa volume?

- correlates with stage
- T3 disease uncommon if volume <0.5 cm³
- LN mets or SV invasion uncommon if volume <4 cm³

What is the Gleason scoring system?

- grading system for PCa } based on glandular pattern of tumour seen at **LOW magnification**
- **no role of cytologic features in grading of tumour**
- primary and secondary patterns reported
- new consensus panel has modified Gleason scoring
 - Gleason score on Bx is NOT THE SAME as scoring on Rad P specimen
 - **on TRUS Bx, primary pattern + highest grade are added to derive Gleason score**
 - **in RP specimens, should mention any tertiary high grade pattern in addition to primary & secondary patterns**

Describe the different Gleason patterns.

- Gleason 1 & 2 } relatively circumscribed nodules of uniform, single, separate, closely packed, medium-sized glands
- Gleason 3 } tumour infiltrates non-neoplastic prostate with marked **variation in size & shape of glands (smaller glands than in Gleason 1 and 2)**
 - } smooth, small, cribriform glands
- Gleason 4 } **glands are no longer single and separate**
 - } may see large, **irregular, cribriform glands**
- Gleason 5 } **no glandular differentiation**
 - } solid sheets, cords, single cells, or tumour with central comedonecrosis

What features may distinguish PCa from normal glands?

- prominent nucleoli
- lack of basal layer
- infiltrative pattern
- darker cytoplasm (more eosinophilic) } different staining quality
- **PCa usually stains +ve for PSA, AMACR** but -ve for HMWK, 34bE12, p63

TRUS Bx

Why should Bx cores be sent in separate containers (CHART)?

- 1) if PIN or ASAP, can preferentially target atypical site on repeat Bx
- 2) if no PCa on initial sampling, pathologists can target additional tissue sampling
- 3) knowledge of site helps pathologists with certain difficult diagnoses (SV tissue may mimic high grade PIN at base; Cowper's gland may mimic PCa at apex)
- 4) with brachy, can target areas for extra seeds
- 5) improves technical aspects of processing specimens
 - helps prevent missing small foci of PCa that can be "buried" in paraffin block
 - prevents core fragmentation

What is the significance of atypia (ASAP) on Bx?

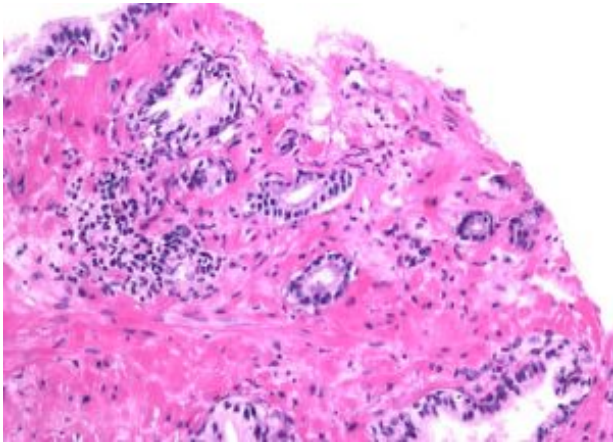
- occurs in ~5% of TRUS Bx specimens
- finding suggestive of PCa but not diagnostic
- previously termed ASAP (atypical small acinar proliferation) } should now be signed out as **"focus of atypical glands"**
- **likelihood of cancer on repeat Bx is ~40-50%**

What are the management options for ASAP found on TRUS Bx? **(AUA Update #35 - 2008)**

- 1) examine multiple deeper tissue sections
- 2) perform immunohistochemistry } p63 (-ve in PCa) & AMACR (+ve in PCa)
- 3) pathology consultation by GU pathologist
- 4) **repeat TRUS Bx (should be done within 3-6 months)**

What other atypical lesions of the prostate have been described? **(AUA Update #35 - 2008)**

- atypical adenomatous hyperplasia (adenosis) → benign and NO repeat Bx recommended
- atypical basal cell hyperplasia → benign and NO repeat Bx recommended
- atypical cribriform glands → similar to ASAP and repeat Bx indicated



→ atypical small acinar proliferation (ASAP)

TURP specimens

What is the significance of adenosis on TURP specimens?

- **atypical adenomatous hyperplasia } benign**
- often confused with low-grade PCa
- usually found in TZ
- often multifocal
- found in 1.6% of TUR specimens and 0.8% of all Bx's

RP specimens

What is the role of whole-mount sectioning of RP specimens?

- more time consuming
- more aesthetically pleasing sections for teaching and publication
- same information can be obtained by routine sections
- on occasion, thinly sliced routine sections may identify +ve margins not seen on whole-mount (which requires thicker slices)

What is the histologic effect of ADT on PCa?

- **causes atrophic changes with immature squamous metaplasia**
- **grade often appears artifactually higher**
- pathologists should not assign a Gleason score to carcinomas with treatment effect

What is the histologic effect of RADs on PCa?

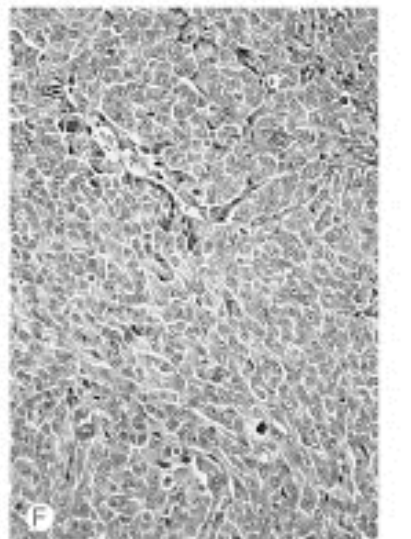
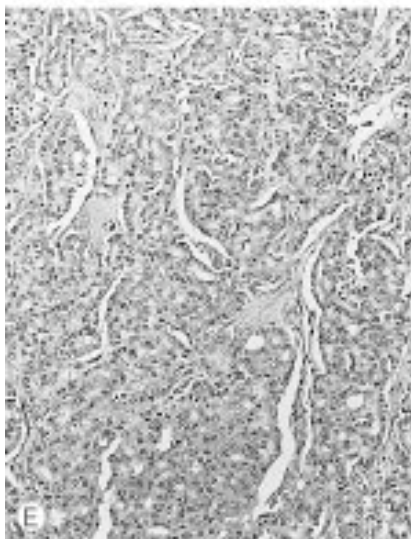
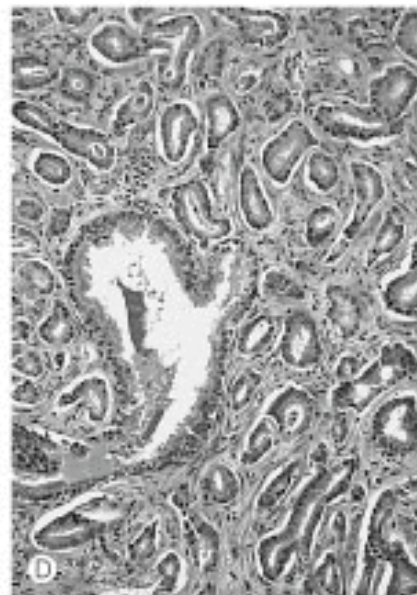
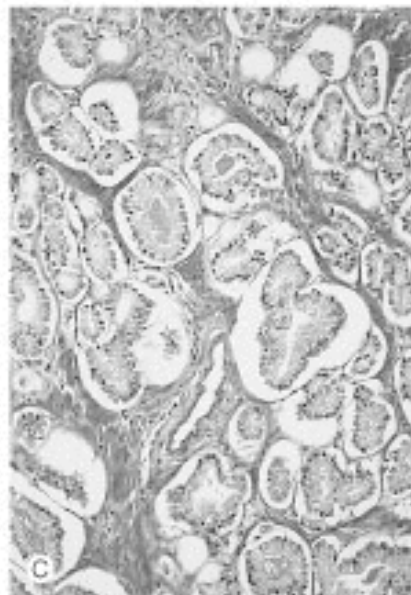
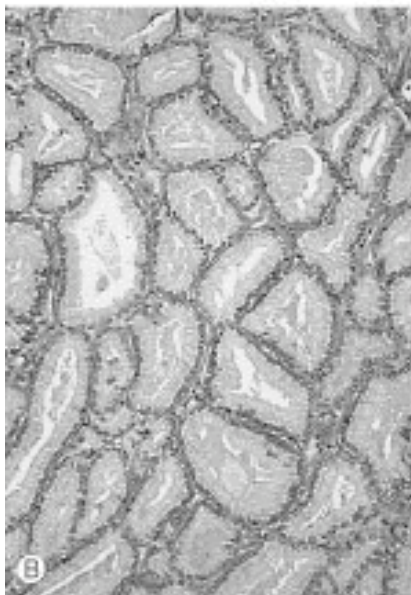
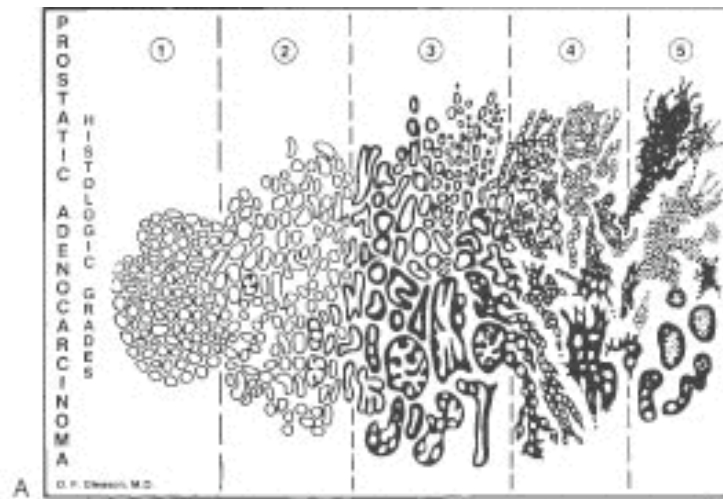
- **alters benign tissue so that it may mimic PCa**
- presence of PCa 12-18 months post-RADs is a predictor of local or distant failure

What is the role of reporting tumour volume on RP specimens?

- does not independently predict post-RP progression once controlling for grade, stage & margin status
- not required on routine RP analysis

What are the indications for aborting a RP at the time of surgery?

- +ve LNs + Gleason 8-10 on TRUS Bx } no benefit from RadP



→ PROSTATIC ADENOCARCINOMA (Gleason patterns 1 (B) through 5 (F))

SUBTYPES OF PROSTATE ADENOCARCINOMA

What are the different subtypes of PCa? } } } “Small Squirmy Men Don’t Like SLTS & Prostitutes”

- 1) **Small cell carcinomas** } 50% are mixed small cell carcinoma & adenocarcinoma
} **doesn’t make PSA (neuroendocrine tumour)**
} **hormone independent**
} **osteolytic mets**
} prostate tumour most responsible for production of **ACTH or ADH**
} **avg survival is <1 year (doesn’t matter whether pure or mixed)**
Rx → **CHEMO** + surgery or RADs
- 4) **Squamous carcinoma (primary)** } rare & has poor prognosis
} develop **osteolytic bone mets**, don’t respond to DES, &
} don’t develop elevated PAP levels with mets
} **usually squamous differentiation occurs in prostate adenocarcinoma that has been treated with DES**
- 1) **Mucinous adenocarcinoma** } one of the least common variants
} **aggressive**
} propensity to develop bone mets & has increased PSA w/ advanced disease
- 3) **Ductal adenocarcinoma** } accounts for <1% of PCa
} may occur in peripheral ducts (like ordinary acinar PCa) but more commonly in TZ (periurethral)
} periurethral ductal PCa can cause obstruction (usually around veru) or hematuria
} PSA not elevated in all cases
} **usually advanced at presentation & aggressive**
→ **should be treated as Gleason 8**
- 9) **Leukemia (primary)** } most common form is **CLL**
- 5) **Sarcoma** } accounts for ~0.1% of prostate cancers
} **rhabdomyosarcoma** is the most frequent mesenchymal tumour of the prostate and almost exclusively found in **kids**
} **leiomyosarcomas** are the most common sarcomas of the **adult** prostate
} carcinosarcomas (sarcomatoid carcinoma) are rare w/ dismal prognosis
- 8) **Lymphoma (primary)** } rare → more commonly have 2° lymphoma of prostate
- 6) **TCC** } primary prostatic TCC (w/o bladder) accounts for 1-4% of all PCa
} more common to find prostatic TCC in patient with hx of bladder TCC (or CIS)
→ if only intraductal TCC present after radical cystectomy, no worse prognosis
→ stromal infiltration worsens prognosis
} stromal invasion almost always present with propensity to invade BN
} **>50% present with T3 or T4 disease while 20% present with mets**
} tend to have **osteolytic bone mets**
Rx → **RADs** for most (high stage), RP for some (if T2)
- 7) **Signet ring cell carcinoma** } >25% of tumour is composed of signet ring cells
→ clear cytoplasm displacing nucleus
} **very aggressive tumour (automatic grade 5)**
- 10) **Phyllodes tumour of the prostate** } stromal/mesenchymal tumour (resembles breast Ca)

Which subtypes of PCa develop OSTEOLYTIC mets? } } } “TSN”

→ **usually get osteoblastic lesions**

- 1) TCC
- 2) Squamous carcinoma
- 3) Neuroendocrine differentiation (small cell)

Which types of tumours develop OSTEOLASTIC bone mets?

- prostatic adenocarcinoma
- multiple myeloma
- stomach
- melanoma (mixed)
- breast Ca (mixed)
- medulloblastoma
- bronchial carcinoid

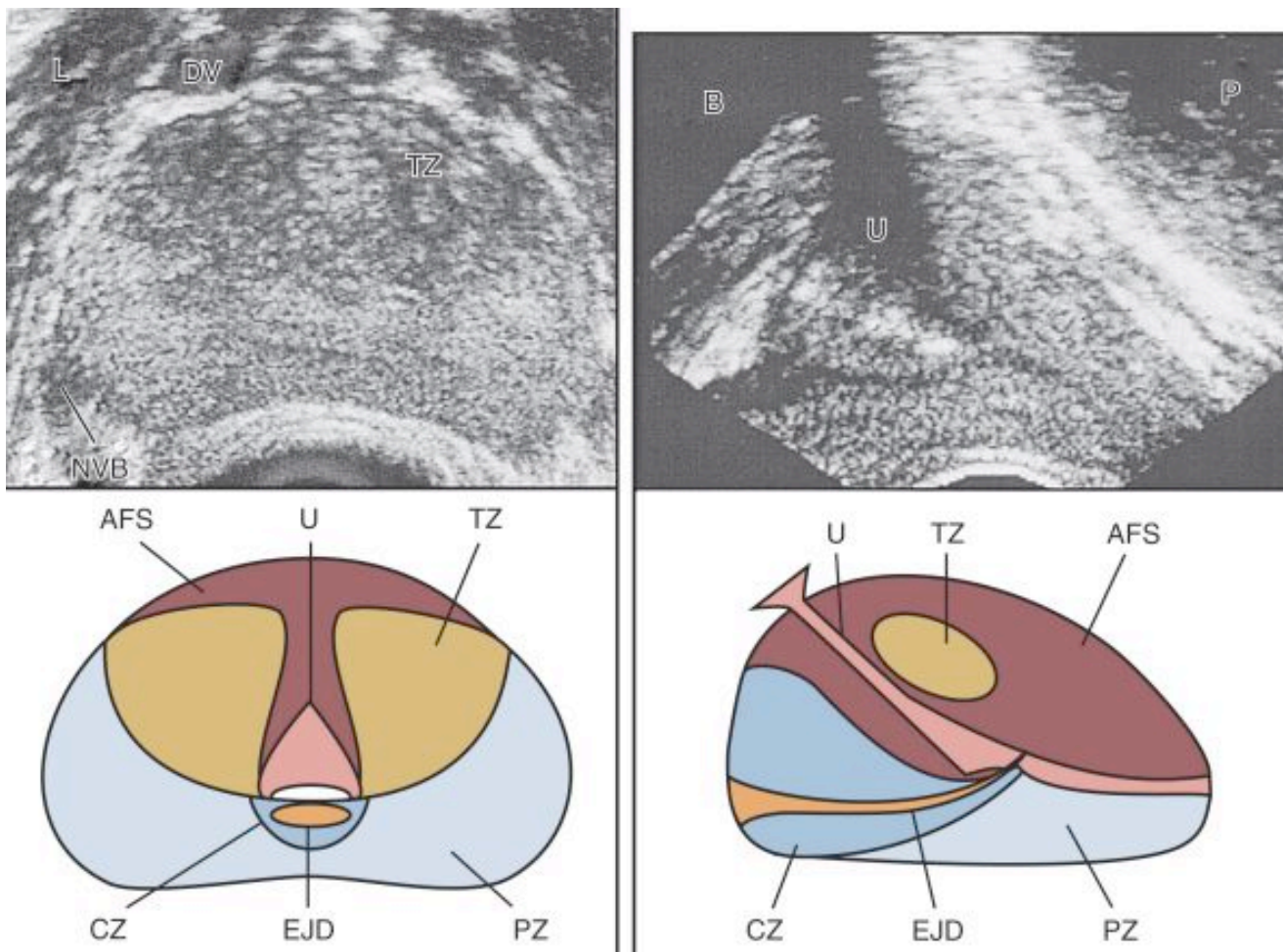
What are the findings suggestive of PCa with neuroendocrine transformation?

- usually are hormone-refractory
- unique expression of receptors similar to other neuroendocrine tumours
 - eg bombesin/gastrin-releasing peptide antagonist, somatostatin, chromogranin A, etc
- usually small cell variant
- 1) frequent visceral mets + rapidly growing soft tissue mets (retroperitoneal disease common)
- 2) relatively low or undetectable PSA
- 3) lytic bone lesions (not the usual osteoblastic pattern)
- 4) brain mets common
- 5) elevated plasma chromogranin levels
- 6) hyperCa (not usually seen)

What is the DDx of small glands seen on TRUS Bx?

- "CABANAS Bx'd the SV"
- **Cancer**
- **ASAP**
- **Basal cell hyperplasia**
- **Atrophy**
- **Nephrogenic adenoma**
- **Atypical adenomatous hyperplasia (adenosis)**
- **Sclerosing adenosis**
- inadvertent **Bx of SVs**

- usually benign



GRAY-SCALE TRUS

What kinds of U/S probes are used for TRUS?

- ➔ **most done with patient in LLD position with images in transverse & sagittal planes**
- end-fire vs side-fire probes
- low frequency transducer (4-MHz) } larger focal range (2-8cm) but lower resolution
➔ good for measuring size
- high frequency transducer (10-MHz) } smaller focal range (1-4cm) but higher resolution
➔ good for Bx

How are lesions characterized on TRUS?

- ➔ **usually compared to PZ**
- hypoechoic (darker than PZ)
- isoechoic
- hyperechoic (lighter than PZ)
- anechoic (completely black)

How does PCa appear on TRUS?

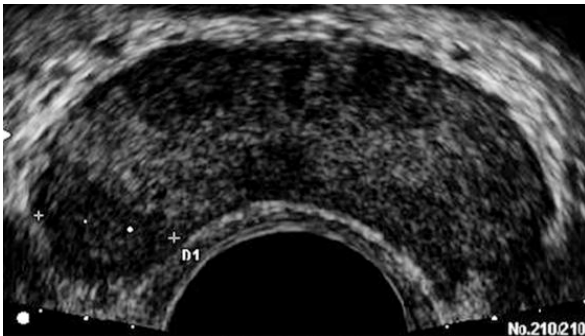
- **most are HYPOechoic** } all hypoechoic nodules should be Bx'd but are not pathognomonic
→ ~20% of hypoechoic nodules are PCa
- up to 40% are isoechoic } **80% of TZ cancers are isoechoic**
- 1% are hyperechoic
- EPE (T3) is suggested if there is a focal loss of typical bright white periprostatic fat on TRUS

What is the DDx of a HYPOechoic lesion on TRUS (black)? } } } THE BLAAC SIGN

- 1) TCC of stroma
- 2) HEmatoma post-Bx
- 3) BPH nodule in TZ
- 4) Lymphoma
- 5) Adenocarcinoma
- 6) Abscess
- 7) Cyst
- 8) Sarcoma (post-RADs)
- 9) Infarcted prostate (atrophy)
- 10) Granuloma post-TB
- 11) Normal tissue

What is the DDx of a HYPERechoic lesion on TRUS (white)? } } } "BAD 3S"

- 1) Brachy seeds
- 2) Adipose tissue (periprostatic)
- 3) Ductal variant tumours
- 4) Stones, calcifications
- 5) SV involvement of tumour
- 6) SCC tumour



→ TRUS } HYPOECHOIC LESION in PZ

How is prostate volume calculated on TRUS?

- most formulae assume prostate is a geometric shape } ellipse, sphere, prolate spheroid
- avg gland is 20-25g until ~age 50, then starts to grow
- calculation involves use of transverse diameter, AP diameter, longitudinal diameter

What is the DDx of a prostatic/SV cyst?

→ **prostatic cysts usually appear anechoic on TRUS with posterior acoustic shadow**

→ congenital ("MPES")

- | | | |
|--------------|--------------------------|---------------|
| a) mullerian | } Mullerian duct cyst | (midline) |
| | } Prostatic utricle cyst | (midline) |
| b) wolffian | } Ejaculatory duct cyst | (off midline) |
| | } SV cyst | (off midline) |

→ acquired

- TZ cyst } from hemorrhagic degeneration of BPH nodule
- PZ cyst

What anomaly is associated with mullerian duct cysts in males?

- unilateral renal agenesis } ABDO U/S mandatory

What anomalies are associated with congenital prostatic utricle cysts?

- 1) hypospadias (most common)
- 2) ambiguous genitalia
- 3) UDT
- 4) congenital urethral polyps

What is the most common reason to Dx ejaculatory duct cysts?

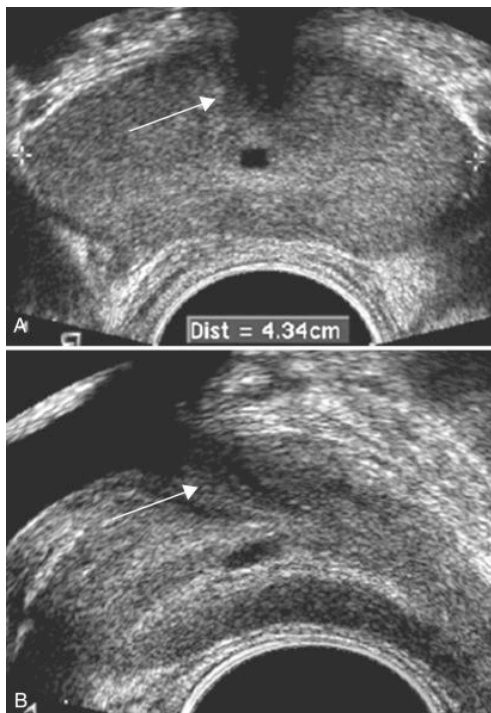
- azoospermia

What anomalies are associated with SV cysts?

- 1) cystic renal disease \ ABDO U/S
- 2) renal agenesis (66%) / mandatory

How does the prostate look on TRUS after treatment?

- 1) EBRT } volume decreases 6 months after Rx
} **diffusely HYPOechoic with poorly defined anatomy**
→ TRUS findings post-RADs correlate poorly with pathologic findings
- 2) brachytherapy } seeds are HYPERechoic + posterior shadowing
} initial edema followed by similar long-term findings to EBRT
- 3) ADT } volume decreases by ~30%
- 4) RP } smooth tapering of the BN to the urethra
} may see a nodule of tissue anterior to the anastomosis
→ ligated DVC
} any hyperechoic or hypoechoic lesions disrupting retroanastomotic fat plane should be considered suspicious
→ no role for Bx with PSA recurrence if no palpable nodule



→ TRUS } EJACULATORY DUCT CYST (midline)

PROSTATE BX TECHNIQUES AND OUTCOMES

What are some PSA derivatives that are used to improve PCa risk assessment?

- age-adjusted PSA
- free-to-total PSA ratio (<0.20)
- PSA velocity (>0.75 ng/mL/year)
- PSA density (>0.15) & PSA density of TZ

What are the indications for TRUS?

- 1) treatment planning **volume** measurements (brachy, cryotherapy, HIFU, BPH therapy)
- 2) volume measurement **during hormonal downsizing** for EBRT or brachy
- 3) placement of fiducial **markers** for EBRT
- 4) evaluation of **obstructive azoospermia** (ejaculatory duct cysts, SV cysts, etc)
- 5) therapeutic aspiration or unroofing of prostatic cysts (**drainage of abscesses**)

What are the indications for TRUS Bx?

- 1) **screening for PCa** in asymptomatic patient with life expectancy >10 yrs AND:
 - high risk (family history or black)
 - abN DRE
 - abN PSA (>0.6 if 40yrs old, >2.5 if <60 yrs, >4 if >60 yrs)
- 2) f/u Bx after Dx of **ASAP or HG PIN** (3-6 months later)
- 3) to Dx **failed RADs/RadP/HIFU/cryotherapy** prior to 2nd line therapy
- 4) Dx of suspected **symptomatic PCa** (bone mets, SC compression, etc)
- 5) prior to intervention in **symptomatic BPH (eg simple prostatectomy)**
- 6) prior to cystoprostatectomy or **neobladder**

What is the risk of PCa on repeat Bx after HGPIN or ASAP?

- HG PIN } ~25%
- ASAP } ~50%

→ **all ASAP should get repeat TRUS Bx w/in 3-6 months } controversy re: PIN**

What are the contraindications to TRUS Bx?

- significant coagulopathy
- painful anorectal conditions
- severe immunosuppression
- acute prostatitis

What is involved in preparing patients for a TRUS Bx?

- 1) Hx } implants, valves, acute prostatitis/UTI, meds, allergies, obtain consent
- 2) stop all anti-coagulants ~1 wk prior (coumadin, plavix, ASA, etc)
- 3) ABx prophylaxis (2-3days)
 - despite antibiotics, risk of bacteremia/sepsis still 0.5%
 - oral fluoroquinolones 1st line
 - iv Abx for pts high risk for endocarditis or prosthetic infection
- 4) fleet enema
- 5) counsel on risks & benefits
 - complications
 - risk of missing PCa } 10-35%

What is the ideal analgesic for TRUS Bx?

- infiltration of LA around nerve bundles
 - topical lidocaine jelly alone suboptimal
 - avoid direct infiltration into prostate } risk of systemic absorption

How do you perform a TRUS Bx?

- 1) positioning
 - LLD position with knees/hips flexed at 90 degrees
 - buttocks flush with end of table
 - **lithotomy preferred for certain indications**
 - a) transperineal Bx
 - b) brachy planning
 - c) placement of fiducial gold markers
 - d) use of color Doppler flow U/S
- 2) TRUS
 - assessment in transverse & sagittal planes
 - volume determination
 - identification & localization of any lesions
- 3) Bx
 - 18-gauge needle core Bx's } Bx's sent as segregated samples

What are the different Prostate Bx techniques?

→ TRUS Bx

- 1) sextant Bx } better than DRE-guided or U/S-guided Bx of specific lesions
} can often miss PCa because doesn't sample posterolateral PZ well
→ **INADEQUATE for PCa DETECTION**
- 2) extended core Bx } improved PCa detection compared to sextant Bx
→ 10, 12, 13 core Bx's } **NOW THE STANDARD**
} focuses on laterally directed cores
- 3) anteriorly-directed Bx } recommended if high index of suspicion but no PCa on initial Bx
→ low-yield otherwise, so not routinely done
- 4) TZ Bx } recommended if high index of suspicion but no evidence of PCa on initial Bx
} may also be included in men with glands >50g
→ low-yield otherwise, so not routinely done
→ **adds 15% yield in PCa detection**
- 5) SV Bx } recommended only if palpably abN, PSA >30 ng/mL, or when considering brachy
- 6) repeat Bx } decreasing rate of PCa detection with repeat Bx's
→ especially if initial Bx was extended core Bx
} saturation Bx might be better option
- 7) saturation Bx } detects more PCa than repeat sextant Bx
} drawback = increased anesthetic req'd & hospital setting needed
- 8) FNA Bx } cheaper, faster, easier, with less morbidity
→ **NOT reliable for grading of PCa**

→ Transperineal Bx

- 1) **for patients without a rectum**
- 2) may be better for repeat Bx's } longitudinal cores allow for more efficient sampling of PZ

→ Transurethral Bx (now not needed as can Bx TZ via TRUS)

What are the rates of PCa detection on repeat Bx?

- depends on technique of Bx (sextant VS extended core VS saturation etc)
- | | | |
|------------------------------------|----------|---|
| - 2 nd Bx after sextant | } 20-35% | \ |
| - 3 rd Bx after sextant | } 10-30% | } 3 rd and 4 th Bx's should be reserved for select patients |
| - 4 th Bx after sextant | } 5-35% | / |

What findings on TRUS are suggestive of ECE (T3) PCa?

→ **<60% sensitivity & TRUS can't detect microscopic ECE**

- 1) irregular capsular bulge
- 2) frank extension of hypoechoic lesion into periprostatic fat
- 3) loss of triangle formed by prostatic apex, urethra, & rectal wall (trapezoid area) on sagittal

What findings on TRUS are suggestive of SV involvement?

- 1) loss of normal "beak" configuration on sagittal view
→ "beak" = angled, tapered junction b/w SV's and base of prostate
- 2) enlarged, HYPER-echoic SV
→ **asymmetry is common and not significant for PCa involvement**

What are the potential complications of TRUS Bx?

- 1) infections } mostly limited to UTI or low-grade febrile prostatitis
→ can also get epididymitis, pyelonephritis
} ~2% risk of requiring iv Abx & hospitalization
} rare cases of fatal septicemia
- 2) bleeding } **most common complication post-TRUS Bx**
} rectal bleeding usually minor and self-limited (2-20%)
→ significant bleeding requiring anoscopic Rx is uncommon (<2%)
} hematospermia and hematuria common (10-50%)
- 3) vasovagal response } occurs in 1-5%
→ stop, place in Trendelenburg, iv fluids, po glucose/candy
- 4) AUR } occurs in <0.5%
→ increased risk with large prostates and high IPSS

ADVANCED U/S FOR THE PROSTATE

What is the role of Color & Power Doppler U/S in imaging the prostate?

→ **improved PCa detection cf grey-scale TRUS**

→ **not good enough to replace TRUS Bx**

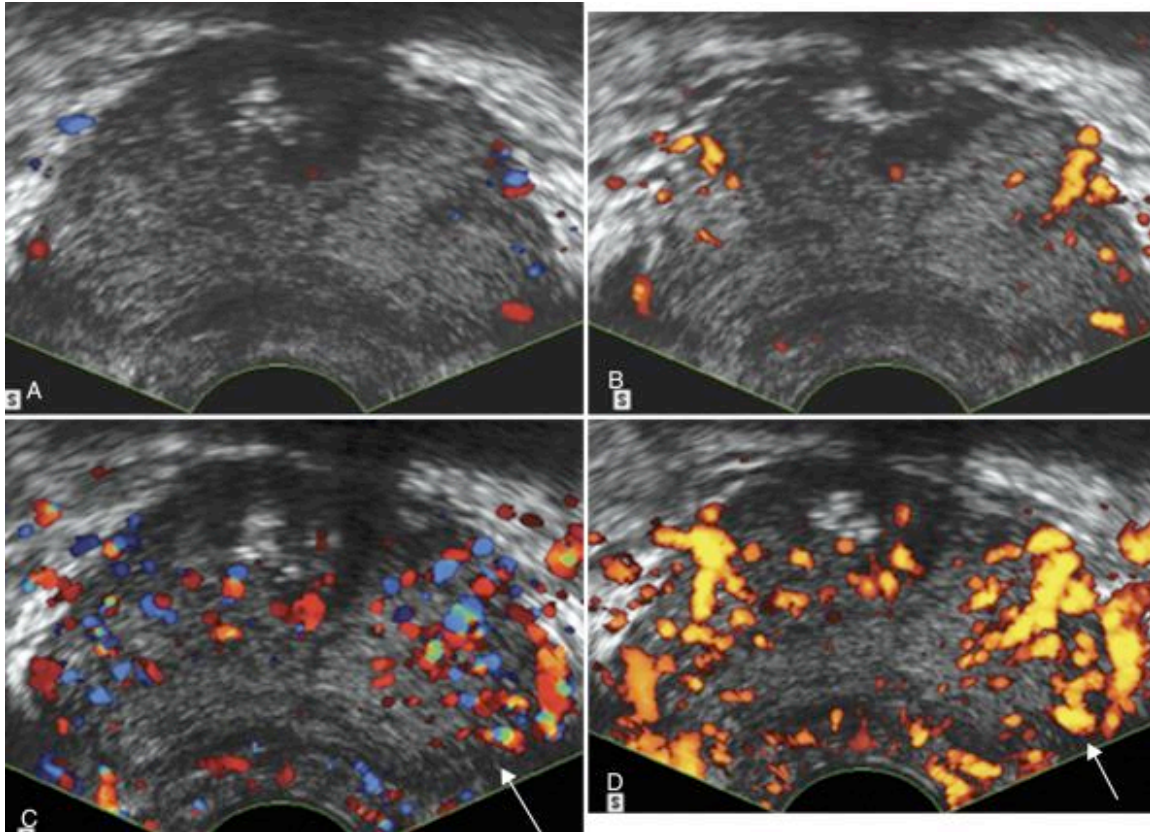
- Color Doppler } detects blood flow
} red = flow toward transducer, blue = flow away from transducer
} PCa foci have increased density of microvessels but **current Doppler technology can only detect larger feeding vessels**
- Power Doppler } detects flow independent of velocity and direction
} good at **detecting PCa neovascularity**

What prognostic features are associated with increased flow on pre-op Color Doppler U/S?

- 10-fold increased risk of PSA recurrence
- higher Gleason grade
- increased incidence of SV invasion
- lower biochemical disease-free survival rate

What other investigational techniques are used to improve U/S detection of PCa?

- 1) iv microbubble contrast agents used to amplify flow signals within microvasculature of PCa
→ "bubble" agents are encapsulated 1-0 µm pockets of air or high-molecular-weight gas
→ improves sensitivity of PCa detection
- 2) automated image analysis using artificial neural networks
- 3) elastography } assesses differences in U/S image during compression
} decreased tissue elasticity = suggestive of PCa
- 4) contrast-enhanced Doppler



- A } UNENHANCED COLOR DOPPLER TRUS
 B } POWER DOPPLER TRUS
 C } MICROBUBBLE COLOR DOPPLER TRUS
 D } MICROBUBBLE POWER DOPPLER TRUS

\ left mid-gland PCa
 / nodule identified

Chapter #93 – PCa Tumour Markers

KALLIKREIN TUMOUR MARKERS

What is the human kallikrein gene family?

- 15 genes have now been identified (chromosome 19q13)
- **family of serine proteases**
 - hk1 (pancreatic/renal/salivary gland kallikrein)
 - hk2 (enzyme that cleaves proPSA) } 80% homology with PSA
 - hk3 (PSA)
- hk2 & hk3 can both be inactivated by forming complexes with **α 1-antichymotrypsin (ACT)**, **α 2-macroglobulin (MG)**, or **α 1-protease inhibitor (API)**
- elevated hk2 associated with high grade PCa
- hk6 & hk10 may be potential biomarker for ovarian Ca

What is PSA?

- **33-kD glycoprotein serine protease first identified by Wang in late 70's**
- function is to liquefy seminal coagulum } acts on semenogelin & fibronectin
- 100-fold higher concentration in semen than blood (ng/mL vs mg/mL)
- found in serum in free unbound form (active) & complexed bound form (inactive)
 - majority in serum is in complexed form (~60-95%)
 - **PSA-ACT detectable (mainly)**
 - **PSA-MG undetectable**
 - **PSA-API detectable**
- **complexed PSA cleared via liver**
- **free PSA cleared via kidney (takes only 2-3 hours) } ESRD pts have higher F/T ratio**
- **PSA $T_{1/2}$ = 2-3 days**
- PSA gene expression increased by DHT, VIP, and GHRH (old exam)

Why is PSA elevated in PCa?

- **prostate cancer cells don't make more PSA than normal prostatic tissue**
 - 1.5-fold lower mRNA expressed in PCa
- elevated PSA likely from cancer progression & destabilization of prostate cellular architecture

What are the significant causes of elevated PSA?

- 1) **PCa**
- 2) **BPH**
- 3) **prostatitis**
- 4) **prostatic infarction**
- 5) **AUR**
- 6) recent ejaculation
- 7) prostate manipulation (Bx, TUR, etc)

} prostate specific but NOT disease specific

What are some ectopic sources of PSA? } "BALKS"

- normal & malignant breast tissue
- breast milk
- female serum
- adrenal carcinomas
- glands of Littre
- renal carcinomas
- Skene's gland tumour

What are the potential causes of a PSA decrease?

- 1) surgery } RP, TURP, HIFU, etc
- 2) RADs
- 3) resolution of prostatitis
- 4) 5ARI therapy
- 5) hormones (anti-androgens, LHRH-analogue, etc)
- 6) surgical castration

What is the average yearly increase in PSA?

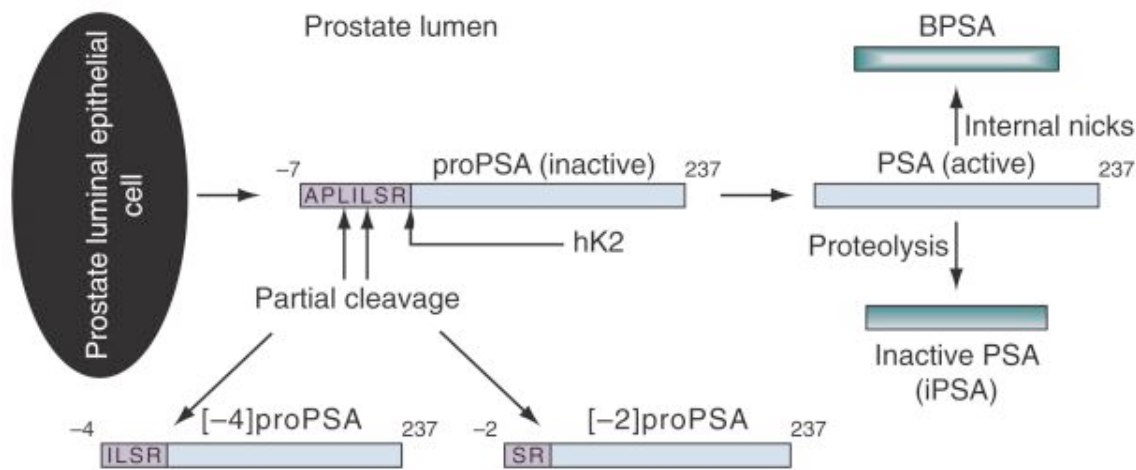
- no BPH } 0.04 ng/mL per year
- + BPH } 0.07 – 0.27 ng/mL per year

What are some PSA derivatives used to increase the specificity of PSA testing?

- likely of no benefit in men with PSA >10 ng/mL due to high likelihood of PCa
- majority of data accrued for PSA range 4-10 ng/mL
- improves sensitivity but risks decreasing specificity } over-investigation & overdetection
- 1) PSA density } PSA/volume ≥ 0.15 associated with PCa
 - limited by variations in TRUS measurements
- 2) PSA velocity } rate >0.75 ng/mL/yr associated with PCa
 - } need at least 3 readings over 18 month period
 - limited by the need for multiple readings
- 3) age-specific PSA } <2.5 ng/mL for men <50yrs of age
 - } <3.5 ng/mL for men <60yrs of age
 - } <4.5 ng/mL for men <70yrs of age
 - may miss significant cancers in older men AND may result in overdetection in younger men
- 4) f/t ratio } ratio <0.10 – 0.25 associated with PCa
 - no accepted cutoff
 - size of prostate, use of 5ARIs, and race may affect f/t ratio

How is PSA formed?

- starts as proPSA } PSA + 7aa leader sequence
- proPSA is cleaved by hK2 into active PSA } cleavage of 7aa leader sequence
 - partial cleavage leads to other forms of free PSA } [-2]pPSA, [-4]pPSA, etc
- majority of active PSA is complexed
 - mainly to α_1 -antichymotrypsin (ACT)
- active PSA can undergo proteolysis to form BPSA or iPSA



→ DIFFERENTIAL CLEAVAGE AND ACTIVATION OF proPSA

What molecular derivatives of PSA have been used to improve detection of PCa?

- a) **free PSA forms (5-40%)**
 - elevated in PCa
 - 1) proPSA (pPSA or [-7]pPSA)
 - 2) [-2]pPSA } from incomplete cleavage and processing of proPSA
 - 3) [-4]pPSA } from incomplete cleavage and processing of proPSA
 - elevated in BPH
 - 4) iPSA } from proteolysis of active PSA
 - 5) BPSA } from internal degradation of active PSA
 - 6) fPSA
- b) **complexed PSA forms (60-95%)**
 - cPSA } elevated in PCa
- c) **other kallikreins**
 - elevated in PCa
 - 1) hk2 (esp in high grade disease)
 - 2) ?hk4 (associated with advanced ovarian Ca)
 - 3) hk14
 - 4) hk15
 - lower in PCa
 - 5) hK11

What is the likelihood of PCa based on PSA? }}} No longer apply (eg PCPT 6.6% PCa in PSA <0.5)

- normal DRE
- PSA <2.5 ng/mL } <2%
- PSA 2.5-4.0 ng/mL } ~18-25% → ~80% chance organ-confined
- PSA 4-10 ng/mL } 25-40% → ~66% chance organ-confined
- PSA >10ng/mL } ~67% → ~50% chance organ-confined

How well does PSA predict PCa stage?

- 80% of men with PSA <4 have organ-confined disease
- 66% of men with PSA between 4 and 10 have organ-confined disease
- >50% of men with PSA >10 have T3 disease
- 20% of men with PSA >20 have +ve LNs
- 75% of men with PSA >50 have +ve LNs
- **rise in PSA of >2.0ng/mL/yr before the diagnosis of PCa associated with increased risk of death after RP (D'Amico et al, NEJM '04)**

PROSTATE-SPECIFIC MEMBRANE ANTIGEN

What is PSMA?

- glycoprotein prostate-specific membrane Ag } type 2 integral membrane protein
- **folate hydrolase** found embedded within cell membrane of prostatic epithelial cells
- small intracellular domain with large extracellular domain
- PSMA is found in prostate, intestine, and CNS } predominantly expressed in prostate

What is the potential clinical use of PSMA?

- **PSMA elevated in PCa**
- Ab's to PSMA used to differentiate PCa from BPH
- PSMA mRNA expression within PCa is highest in castrated state
- PSM' (differentially expressed variant) levels lower in PCa

MOLECULAR BIOLOGY AND DISCOVERY OF SERUM BIOMARKERS FOR PCa

What are some of the susceptibility genes associated with the development of PCa?

- **HPC1 (1q24-25)**
- PcaP (1q42)
- CAPB (1p36)
- PON1 (7q21)
- MSR1 (8p22-23)
- HPC2 (17p11)
- HPC20 (20q13)
- HPCX (Xq27-28)

What genetic polymorphisms suggest a role of infection & inflammation in the development of PCa?

- 1) androgen receptor (AR) genes
- 2) CYP17 genes
- 3) 5 α -reductase type 2 genes (SRD5A2)

What other genetic polymorphisms are associated with the development of PCa?

- GST-P1
- IGF
- CYP3A

What genes/proteins have been found to be upregulated (overexpressed) in PCa tissue?

- **AMACR gene** (chromosome 5)
- **DD3 PCA3 protein** (chromosome 9) } found in 95% of PCa and PCa mets specimens
- UROC28 gene (chromosome 6)
- hepsin protein (serine protease)
- NMP48 protein

What is the significance of CpG islands?

- segments within the gene promoter that are composed of GC-rich regions
 - alterations in methylation status of CpG islands affect gene expression and play a role in carcinogenesis
 - hypermethylation associated with PCa
- **hypermethylation of GSTP1 & RASSF1A genes are also assoc'd w/ PCa development**

Chapter #94 – Diagnosis and Staging of PCa

DETECTION OF PROSTATE CANCER

How does PCa usually present?

- **>80% asymptomatic** (elevated PSA or abN DRE) } stage migration effect of PSA screening
- majority of PCa arises in periphery and so are asymptomatic
- locally advanced } LUTS, hydronephrosis, ED (NVB invasion), hematospermia, ↓'d ejaculate volume
- metastatic disease } bone pain, renal failure, anemia, lower limb edema, malignant RPF, paraneoplastic syndromes, DIC

What paraneoplastic features can be present in PCa?

- anemia
- cachexia
- hyperCa
- hyperPO₄
- Cushing's } ectopic ACTH
- coagulation disorders (eg DIC)
- SIADH
- gynecomastia } ↑'d βhCG
- neuromuscular symptoms } necrotizing myelopathy, symmetrical proximal muscle weakness, cerebellar signs, diplopia, etc
- dermatomyositis (rare)

What are the main concerns about PCa screening?

- 1) lifetime risk of PCa is ~17% while the lifetime risk of death from PCa is ~3% (SEER data)
 - screening may result in overdiagnosis (detection of indolent disease) & over-Rx of some men
- 2) screening more common in older men
 - detection & treatment of PCa in older men may not extend life
- 3) screening may result in false +ve screens, resulting in unnecessary TRUS Bx's and treatment of PCa with unwanted side effects
 - not worth the cost if detecting & treating indolent disease
- 4) costs of screening may not be justified if societal harm of Dx and Rx is far greater than any health benefits obtained

➔ ISSUES FOR ALL SCREENING PROGRAMS, NOT UNIQUE TO JUST PCa

What is the role of PSA screening?

- US Preventive Services Task Force (2002)
 - insufficient evidence to recommend for or against routine screening for PCa using PSA or DRE
- American Cancer Society & AUA
 - recommends PCa screening with PSA + DRE be offered to all men >50yrs of age
 - discuss risks & benefits of screening with patient
- mortality rates of PCa have declined by 27% between 1991 and 2001
 - decrease in distant mets mortality due to a decline in distant mets incidence not due to improved survival of patients with distant mets
 - earlier detection and treatment before PCa becomes metastatic had a greater impact than improvements in the treatment of advanced disease
 - BUT, mortality reductions may be due to changing risk factors, attribution bias, and greater use of hormones

*** STILL CONTROVERSIAL ***

What randomized trials have been conducted to evaluate the value of PSA screening?

- 1) Quebec prospective RCT (Labrie et al, Prostate '04)
 - 46,486 men between 45 and 80yrs of age
 - endpoint was PCa-specific mortality
 - invited vs not invited for PSA screening
 - in screened arm, PSA >3 or abN DRE were indications for Bx
 - 11yr follow-up showed **62% reduction in PCa-specific mortality in screened arm**
 - BUT, not truly randomized study
 - compared invited & volunteered for screening VS not invited & did not undertake screening on their own initiative
 - only 24% of invited group was actually screened
 - intention to treat analysis showed insignificant relative risk of 1.08 associated with screening
- 2) PLCO trial by NCI (US)
 - multi-centre, large-scale randomized trial to evaluate effectiveness of PCa screening in men ~50 to 74yrs of age
 - finished accrual in 2001
 - ~38K men in each arm
 - yearly PSA x 5yrs and yearly DRE x 3yrs } for-cause Bx's not all getting done
 - could affect outcomes
 - followed for at least 13 yrs
 - endpoint is PCa-specific mortality
 - *** AWAITING RESULTS in 2009 ***
- 3) European Randomized Screening for PCa (ERSPC) trial
 - multi-centre, large-scale randomized trial to evaluate effectiveness of PCa screening in men 55-69yrs of age
 - 165K men total
 - 4yr rescreening interval in most centres
 - endpoint is PCa-specific mortality
 - *** AWAITING RESULTS in 2009 ***
 - \ } early subset analysis (Rotterdam)
 - / } shows benefit of screening

DIAGNOSTIC MODALITIES

What is PSA?

- enzyme in human kallikrein gene family produced by epithelium } serine protease
- chromosome 19
- secreted in high concentrations (mg/mL) into seminal fluid to help liquefy seminal coagulum
- normally found in low concentrations in serum (ng/mL)
 - 60-95% bound (complexed) & 5-40% unbound (free)
- PSA expression is strongly influenced by androgens
 - also affected by age, race, prostate volume, meds (eg 5ARIs)
- lower levels seen in elderly (testosterone) and obese men (estrogen)
- higher levels seen in men with BPH and in blacks
- cleared through liver } **half-life is 2-3 days**
 - } free PSA is cleared by kidneys (2-3hrs)

What are the main enzymes of the kallikrein family?

- hK1 } expressed in prostate, kidney, pancreas, and salivary glands
- hK2 } expressed mainly in prostate (cleaves pro-PSA into active PSA)
- **hK3 } PSA**

How does PSA circulate within serum?

- circulates in both bound (complexed) & unbound (free) forms
- 60-95% bound to α 1-antichymotrypsin (ACT), α 2-macroglobulin (MG), or α 1-protease inhibitor (API)
 - mostly ACT
 - PSA bound to MG is undetectable
- 5-40% found in free, unbound form

How is PSA secreted into serum?

- secreted from prostatic luminal epithelium as pPSA or proPSA (with 7aa leader sequence)
- proPSA cleaved by hK2 into active free PSA (fPSA) or partially cleaved into different isoforms of fPSA
- fPSA can be further cleaved to BPSA or inactive PSA (iPSA)
 - fPSA, BPSA, iPSA more common in BPH
 - proPSA, hK2 more common with PCa

What is the role of 5 α -reductase inhibitors on PSA levels?

- should decrease PSA by ~50% after 12 months of therapy
- both finasteride & dutasteride lower PSA to the same extent
- 1mg dose of finasteride (Propecia) results in same decline in PSA as 5mg dosage (Proscar)
- if PSA doesn't decrease by 50% or if there is a rise in PSA while on 5ARIs must r/o PCa
- **5ARIs DO NOT affect f/t ratio of PSA**

What is the avg yearly increase in PSA for men?

- no BPH } 0.04 ng/mL per yr
- + BPH } 0.07 – 0.27 ng/mL per yr

What are the common PSA levels found in men of different ages?

- PSA \leq 2.5 } 88% of men 50-60 yrs
 - } 75% of men 60-70yrs
 - } 61% of men >70yrs
- PSA 2.6 - 4.0 } 8% of men 50-60yrs
 - } 14% of men 60-70yrs
 - } 18% of men >70yrs
- PSA >4.1 } 4% of men 50-60yrs
 - } 11% of men 60-70yrs
 - } 21% of men >70yrs

How is PSA as a screening test?

- 1) effectiveness debated
 - may not improve survival
- 2) more effect than DRE alone and most effective when combined with DRE
 - would miss almost 50% of PCa if using DRE alone
 - **BUT, would miss ~17% of PCa if using PSA alone**
- 3) increased detection rates of PCa
- 4) leads to detection of PCa that are more likely to be organ confined
 - DRE-detected PCa more likely to be high grade and locally advanced
 - stage shift favoring localized disease occurred after PSA screening introduced
- 5) elevated PSA has the highest +ve predictive value for PCa
 - more PCa on Bx due to elevated PSA when compared with abN DRE or TRUS
- 6) BUT, concern is that PSA screening will result in detection of indolent disease and lead to overtreatment of low-risk PCa with very favorable prognosis

How good is DRE as a screening test for PCa?

- **DRE alone misses 44% of PCa**
- PSA improves the PPV of DRE for PCa
- PPV increases directly with PSA level and also depends on age and race

What is the chance of PCa based on PSA and DRE findings (CHART)?

PSA	DRE	PCa on Bx	High-grade PCa on Bx
0-2	normal	~10%	1-2%
2-4	normal	~20-25%	2-5%
4-10	normal	25-40%	~5%
	abN	15-60%	10-20%
>10	normal	45-65%	~20%
	abN	70-90%	~50%

What is the evidence that PSA + DRE is better than DRE alone in screening for PCa?

- 1) Catalona et al '94
 - 6630 men } TRUS BX if PSA >4 or abnormal DRE
 - PSA detected more tumors (82%) than DRE (55%)
 - pathologically organ confined disease in 71%
 - **majority of cancers detected by DRE + PSA are organ confined**
 - PSA + DRE increased detection of organ confined disease by 78% over DRE alone
- 2) Chodak et al '89
 - 2131 men >45yrs of age
 - DRE alone as screen for PCa } TRUS Bx if induration, asymmetry, or nodules
 - 144 men got Bx & 36 men had PCa
 - organ-confined disease in only 32%
 - **majority of cancers detected by DRE alone are advanced**
 - 50% pathologic upstaging after RP

What are the different methods of improving PSA as a screening tool?

- 1) age-adjusted PSA
 - threshold of 4.0 ng/mL for men >50yrs
 - threshold of 2.5 ng/mL for men 40-50yrs
 - low threshold } miss less cancers but overdiagnose
 - high threshold } don't overdiagnose but will miss cancers
- 2) ethnicity-adjusted PSA
 - usually higher for blacks and lower for asians
- 3) PSA density
 - **≥0.15** (for PSA between 4 - 10 & normal DRE) associated with higher risk of PCa
 - would miss 30-50% of PCa if using this threshold only
- 4) TZ volume-adjusted PSA
 - attempt to control for BPH from mainly TZ
 - ≥0.23 ng/mL/cm³ (if TZ >20cm³) associated with higher risk of PCa
 - ≥0.38ng/mL/cm³ (if TZ <20cm³) associated with higher risk of PCa
- 5) PSA velocity
 - rate **>0.75ng/mL per year** associated with PCa
 - only 5% of men without PCa had a PSA velocity >0.75 (cf 72% for men with PCa)
- 6) free-to-total ratio of PSA
 - PCa associated with higher complexed PSA
 - risk of PCa **higher for f/t ratio <10% & much lower for f/t ratio >20%**
- 7) molecular derivatives of PSA
 - measurement of complexed PSA alone (cPSA) may have a role also
 - cPSA elevated in PCa
 - cPSA found to be better than total PSA in some studies
 - use of proPSA or pPSA
 - also elevated in PCa
 - other kallikrein markers
 - hK2 elevated in PCa
 - benign markers also
 - BPSA, iPSA higher in BPH

How good is TRUS as a screening test for PCa?

- <20% of hypoechoic lesions on TRUS contain PCa
→ but ~60% of PCa lesions appear hypoechoic on TRUS
- 50% of nonpalpable tumours >1cm are NOT seen on U/S

What are 9 things that can appear hypoechoic on TRUS? }}} “THE BLAAC SIGN “

- 1) TCC of stroma
- 2) HEMatoma post-Bx
- 3) BPH nodule in TZ
- 4) Lymphoma (usually secondary)
- 5) AdenoCarcinoma
- 6) Abscess
- 7) Sarcoma (post-RADs)
- 8) Infarcted prostate (atrophy)
- 9) Granuloma post-TB
- 10) Normal tissue

What are 6 things that can appear hyperechoic on TRUS? } } } “BAD SSS”

- 1) **Brachy seeds**
- 2) **Adipose tissue (periprostatic)**
- 3) **Ductal variant adenoCa**
- 4) **Stones/calcifications**
- 5) **SV involvement**
- 6) **Squamous cell carcinoma**

GUIDELINES FOR EARLY DETECTION OF PROSTATE CANCER

When should screening for PCa start?

→ optimum age at which to begin not yet determined

- AUA recommendations } offered annually starting at age 50yrs
 } earlier for those at higher risk (family hx, blacks at age 40)
- NCCN } recommends all men be offered PSA screening starting at age 40yrs
 } frequency of f/u should depend on PSA results

Why might PSA screening be more beneficial in younger men?

- 1) most of the PCa deaths occurring in men aged 50-64yrs may have been prevented by detection and treatment when they were in their 40's
- 2) younger men more likely to have curable PCa & may have improved disease-free outcomes
- 3) PSA is more specific in younger men, who are less likely to have BPH
- 4) because PCa progresses slowly, it may not be necessary to screen younger men as often (screening frequency could be based on baseline PSA)

What is the most cost-effective approach to PCa screening?

→ Ross et al, JAMA '00

- used Markov model of the natural hx of PCA
- annual PSA starting at age 50yrs not ideal
- PSA tests at age 40, 45, then q2yrs starting at age 50 with threshold of 4ng/mL
used fewer resources and saved more lives

→ many other studies suggest different screening intervals based on an early baseline PSA

- Carter et al '97, Hugosson et al '03, Cruijsen-Koeter et al '03

What is the recommended interval between PCa screenings?

- AUA, American Cancer Society, NCCN
 - annual screening for all men >50yrs of age
- Carter et al, JAMA '97, Hugosson et al, J Urol '03
 - screening q2yrs for men with PSA levels of ≤ 2 ng/mL, annual screening if > 2 ng/mL
- van der Crujisen-Koeter et al, '03
 - screening q4yrs maybe reasonable, depending on baseline PSA

When should screening for PCa be discontinued?

- **classically, screening for men only with a life expectancy of >10yrs recommended**
- benefits of screening decline rapidly with age
- may be more cost-effective to screen only until age 65
 - even men with non-screen-detected PCa don't die before 15yrs without Rx
- may be reasonable to discontinue screening before age 70 for most men who have been involved in a screening program with PSA levels consistent with a low risk of PCa
 - risk of missing significant PCa in man with PSA < 1.0 ng/mL at age 65 is very low

What is the role of repeat Bx?

- **should consider repeat Bx if high index of suspicion even after an initial normal Bx**
 - abN DRE, very high PSA, rising PSA, poor PSA derivatives (F/T ratio, PSA density, PSA velocity, etc)
- **Bx of TZ not recommended at initial Bx, but should be included in repeat Bx's**
- 90% of PCa detected by performing 2 sextant biopsies
 - so likelihood of missing a life-threatening PCa is unlikely after 2 Bx's
- **consider repeat Bx for ASAP but likely not for PIN**
 - risk of PCa on repeat Bx after ASAP is ~40-50%
 - risk of PCa on repeat Bx after PIN is about same as risk after negative 1st Bx (20-25%)
- no guarantees re: the need for future Bx if any change in DRE, PSA kinetics, etc

STAGING OF PROSTATE CANCER

What is the goal of PCa staging?

- to determine the extent of disease as precisely as possible to **assess prognosis & guide Rx**
 - to utilize pretreatment parameters to predict the true extent of disease
- local extent determined by DRE (T stage), serum PSA level before Bx, and tumour grade on Bx correlate directly with pathologic extent of disease

What is the TNM staging of PCa (2002 AJCC)?

- T stage
 - T1a } PCa found after TURP with $< 5\%$ involved or \leq Gleason 6
 - T1b } PCa found after TURP with $> 5\%$ involved or \geq Gleason 7
 - T1c } PCa found on TRUS Bx
 - T2a } palpable PCa involving $\leq 50\%$ of one lobe
 - T2b } palpable PCa involving $> 50\%$ of one lobe
 - T2c } palpable PCa involving both lobes
 - T3a } ECE
 - T3b } SV invasion
 - T4 } invasion of BN, external sphincter, rectum, levators, and/or pelvic wall
- N stage
 - N1 } mets in regional LNs *** old system had N1, N2, N3 based on # and size of nodes ***
- M stage
 - M1a } involvement of non-regional LNs
 - M1b } involvement of bones
 - M1c } involvement of other distant sites

What is the old Whitmore-Jewett staging system for PCa?

- Stage A1 } PCa found after TURP with <5% involved or Gleason ≤7
- Stage A2 } PCa found after TURP with >5% involved or Gleason >7
- Stage B1 } single nodule involving one lobe
- Stage B2 } more extensive involvement of one lobe or involvement of both lobes
- Stage C1 } ECE or SV invasion
- Stage C2 } invasion of adjacent structures
- Stage D0 } elevated PAP
- **Stage D1 } involvement of regional LNs**
- **Stage D2 } distant mets (non-regional LNs, bones, etc)**
- **Stage D3 } HRPC**

What findings on TRUS Bx are used to predict long-term outcome after treatment of PCa?

- 1) Gleason grade **(most important)**
- 2) extent of disease } # of +ve cores
 } % of +ve cores
- 3) SV involvement
- 4) invasion of periprostatic tissue
- 5) perineural invasion (predicts for ECE on RadP, may predict also for LN +ve disease)

What are the clinical criteria that predict pathologic stage & long-term outcomes after treatment?

→ Partin tables and Kattan nomograms

- 1) clinical T stage based on DRE
- 2) PSA level
- 3) Gleason grade

What are the different risk groups for PCa based on pre-treatment clinical parameters?

➔ D'Amico et al '01 (MSK)

- low-risk } ≤T2a, PSA ≤10, AND Gleason ≤6
 → disease-free survival at 10yrs post-RP = 83%
- intermediate-risk } T2b OR PSA 10-20 OR Gleason 7
 → disease-free survival at 10yrs post-RP = 46%
- high-risk } ≥T2c OR PSA >20 OR Gleason ≥8
 → disease-free survival at 10yrs post-RP = 29%

What are the pathologic criteria that predict prognosis after RP?

→ more accurate predictor of prognosis than pretreatment clinical parameters

→ **pathologic stage predicts biochemical recurrence-free survival rate & cancer-specific survival rate**

- 1) Gleason grade
- 2) surgical margin status
- 3) presence of extracapsular disease
- 4) SV invasion
- 5) pelvic LN involvement

How well does PSA predict PCa stage?

- 80% of men with PSA <4 have organ-confined disease
 - 66% of men with PSA between 4 and 10 have organ-confined disease
 - >50% of men with PSA >10 have T3 disease
 - 20% of men with PSA >20 have +ve LNs
 - 75% of men with PSA >50 have +ve LNs
- **rise in PSA of >2.0ng/mL/yr before the diagnosis of PCa associated with increased risk of death after RP (D'Amico et al, NEJM '04)**

What are the different methods used to stage PCa?

- 1) DRE
- 2) PSA
- 3) TRUS Bx grade
- 4) combined clinical data } Partin tables, Kattan nomograms
- 5) imaging
- 6) surgery } pelvic LND
- 7) monoclonal Ab nuclear scans (ProstaScint)
- 8) molecular staging

What imaging modalities are used to stage PCa?

→ **limitation of all imaging studies is the inability to image microscopic disease**

- CXR } low-yield exam because lung mets are very rare without widespread mets
- bone scan } most sensitive test for detection of bone mets
- bone xrays } inadequate (only shows lesions when >50% of bone density is replaced by tumour)
- CT scan } low sensitivity
- MRI } low sensitivity
 - } MRI spectroscopy or endorectal MR may help for local staging
- TRUS } insensitive method for detecting local extension of tumour

What are the indications for staging imaging tests?

- 1) bone scan } uses of ^{99m}Tc -MDP (methylene diphosphonate)
 - PSA >20
 - Gleason ≥ 8
 - T3 disease
 - bone pain
- 2) CT
 - locally advanced disease on DRE
 - PSA >20
 - Gleason ≥ 7
 - likely overused

What is the DDx of a +ve bone scan?

- PCa mets
- other malignancy (breast, stomach, lung)
- osteomyelitis
- Paget's disease
- metabolic bone disease
- degenerative joint disease
- trauma

What is the DDx of a "superscan" on bone scan for PCa?

- diffuse bony mets } kidneys don't light up very well
- Paget's disease
- renal failure
- hyperPTH
- hematologic disease with marrow expansion

What features help distinguish metastatic PCa from Paget's disease?

→ PCa

- pain is prominent
- axial skeleton is most common
- osteoblastic
- serum tests may not be elevated

→ Paget's disease

- seldom painful (until late)
- pelvis is most commonly area
- osteolytic or osteoblastic
- ALP markedly elevated & Ca/PO₄ is N
- cortical thickening with intact periosteum
- urine hydroxyproline elevated

What is a ProstaScint scan?

- use of **radiolabeled monoclonal Ab to PSMA**
 - PSMA Ag expressed to a greater degree in PCa cells
- PSMA Ab has $T_{1/2} = 67\text{hrs}$
- identifies microscopic PCa deposits in regional and distant sites } limited accuracy in detection of LN mets
 - sensitivity 62%
 - specificity 72%

What is the role of molecular staging of PCa?

- detection of circulating PCa cells either directly through centrifugation/immunostaining methods or indirectly by identifying mRNA for prostate-specific biomarkers such as PSA or PSMA from circulating prostate cells
 - PCR assays
 - used as evidence of incurable, extra-prostatic disease
- strong predictors of pathological stage
- BUT variable sensitivity in detecting circulating PCa cells
 - in one study, 25% of M found to have organ-confined disease after RP had +ve PCR-PSA assay
 - would have been denied RP

How common is pelvic LN mets?

- correlates with T stage, PSA level, and Gleason grade
- rate of LN mets has declined ever since introduction of PSA screening from 20-40% in 1980's to <6% today
- 20% of men with PSA >20 have +ve LNs
- 75% of men with PSA >50 have +ve LNs

What are the indications for laparoscopic pelvic LN dissection prior to treatment for PCa?

- ➔ **similar indications to do pelvic LND during RP**
- Gleason ≥ 8
- extraprostatic disease on DRE
- PSA >20
- suspicion of enlarged LNs on imaging

How does PCa mets to the lung look like on imaging?

- **diffuse lymphangitis**

Chapter #95 – Localized Prostate Cancer

BACKGROUND

How common is PCa?

- most common non-cutaneous cancer among men
- 3rd leading cause of death from cancer in Canada } lung is 1st, colon 2nd
→ 2nd leading cause in US
- autopsy study (Sakr et al '93) shows microfoci found in ~25% of men in 40s and 75% of men in 80s
→ PCPT ... 25% of men with PSA <4
- 1 in 6 men are diagnosed during lifetime, risk of dying from PCa is 1 in 36
- only 16% of men diagnosed with PCa die from it
- 90% of cases present with localized PCa

What are the main criteria to consider when selecting appropriate treatment for PCa?

- tumour's potential aggressiveness
- patient's general health/co-morbidities
- patient's life expectancy
- QOL preferences of patient

What factors predict the aggressiveness of PCa?

- staging } DRE, imaging, etc
- PSA } total, velocity, doubling time, density, free-to-total ratio, etc
- Gleason score
- # of cores +ve
- volume of cancer in cores
- perineural or LV invasion
- ductal or neuroendocrine differentiation

CONSERVATIVE MANAGEMENT

What is the difference between WW and active surveillance?

- WW } monitoring until development of mets that requires palliative treatment
 - **no intent to cure**
 - goal is to limit morbidity from disease & therapy
- AS } delayed primary therapy until there is evidence of progression
 - **intent to cure persists**
 - goal is to distinguish clinically insignificant PCa from life-threatening PCa while still localized
 - avoid overRx while administering curative Rx when indicated

What is the traditional indication for active surveillance of PCa?

- men with life expectancy <10 yrs & low-grade PCa
 - now being offered to younger patients with low volume, low grade PCa

What evidence exists for WW?

- **most early stage PCa patients have an indolent course for 10-15yrs**
- **substantial increase in local tumour progression & aggressive mets after 10-15yrs**
- overall survival depends strongly on stage and grade, as well as age of patient
- Chodak et al, NEJM '94
 - 828 men from 6 different non-randomized studies
 - WW + delayed hormones } no RP, no RADs
 - 10yr mortality for low-grade PCa was only 13% but 66% for high-grade PCa
 - 10yr risk of mets depends on Gleason grade } 19% for low-grade, 42% intermediate-grade, 74% high-grade
- Johansson et al, JAMA '04
 - population-based cohort study
 - 223 men with ≤clinical T2 PCa diagnosed on TURP or DRE } non-screened men
 - most cancers have indolent course during first 10-15yrs
 - progression-free survival, mets-free survival, PCa-specific survival much worse b/w 15 to 20yrs
 - only high-grade PCa group had excess PCa-related mortality earlier on
 - grade was strongest predictor of survival on multivariate analysis
- Albertsen et al, JAMA '05
 - retrospective population-based, cohort study
 - 767 men b/w ages 55 to 74yrs with ≤clinical T2 PCa (central path review by Gleason)
 - observation OR hormones (immediate or delayed)
 - men with low-grade PCa have minimal risk of death from PCa during 20yrs of f/u
 - men with high-grade PCa have high risk of death within 10yrs

What evidence exists that RP makes a difference?

- Bill-Axelsson et al, NEJM '05 (update of Holmerg NEJM)
 - Scandinavian Trial with 695 men with clinically localized PCa } **unscreened men**
 - randomized to RP or WW (with systemic Rx once symptomatic progression)
 - primary endpoint was death from PCa } median f/u was 8.2yrs
 - 50 deaths in WW arm vs 30 deaths in RP arm (relative HR of 0.56)
 - RP arm had lower relative risk of distant mets (relative HR 0.60)
- Lu-Yao et al, Lancet '97
 - ~60,000 men from SEER database with PCa
 - 10yr PCa-specific survival was higher for RP than WW or RADs } esp for high grade

What is the Epstein criteria for low-risk (“insignificant”) PCa?

- 1) Gleason ≤ 6
 - 2) PSA density $< 0.15 \text{ ng/mL}$
 - 3) ≤ 2 needle cores +ve (minimum 6 total cores)
 - 4) $< 50\%$ in any +ve core
 - 5) f/t ratio ≥ 0.15 } ADDED in 1998
- ~16% of men in original series (Epstein et al 1994) had “insignificant” PCa
→ 94% PPV for insignificant PCa

What is the Kattan criteria for indolent PCa?

- 1) organ confined
 - 2) $< 0.5 \text{ mL}$ tumour volume
 - 3) Gleason ≤ 6
- Kattan et al 2003

What are the Kattan nomograms for indolent PCa?

- **statistical model used to predict presence of indolent PCa** (Kattan et al, J Urol '03)
- based on > 400 men who underwent RP } 20% of low-risk PCa group had “indolent disease”
 - point system from 0 to 200 and includes **7 variables** } **higher score = indolent PCa**
 - 1) pre-treatment PSA
 - 2) clinical stage
 - 3) primary Gleason score
 - 4) secondary Gleason score
 - 5) U/S volume of prostate
 - 6) mm of cancer
 - 7) mm of non-cancer

What are the main criticisms of active surveillance?

- 1) patient anxiety
- 2) misrepresentation/inaccuracy of Bx } 20-30% upstaging
- 3) repeat Bx morbidity } complications of Bx, effect on difficulty of future RP
- 4) progression with potential loss of opportunity for cure
- 5) unclear trigger points for intervention
- 6) often delays treatment by only a few years } putting off the inevitable
- 7) unknown appropriate f/u while on active surveillance

How common is progression while on active surveillance?

- NO GOOD LONG TERM STUDIES TO DATE
- 25-50% develop evidence of progression within 5yrs
 - progression less likely if no PCa on repeat Bx's
 - **Bill-Axelsson et al, NEJM '05**
 - 695 men with $\leq \text{T2}$ PCa
 - randomly assigned to RP vs WW
 - higher rate of local progression, mets, and death from PCa in WW group
 - shorter cancer-specific and overall survival in WW group
 - small absolute risk reduction in mortality but substantial reduction in risk of mets and local progression
- *** but ... WW GROUP INCLUDED MORE THAN JUST LOW-RISK/EPSTEIN PTS ***

What evidence exists that active surveillance is safe?

→ no great RCTs

→ **Carter et al, J Urol '02 (Walsh/Epstein)**

- cohort of 81 men with stage T1c PCa (Epstein criteria)
- median f/u of 23 months
- DRE and PSA q6mos & repeat Bx q1yr
- progression defined based on f/u Bx:
 - Gleason 4 or 5
 - ≥3 cores +ve
 - >50% involvement of a core

- **31% progression** } **56% had progression if every f/u Bx showed PCa**
 } **only 7% of men with ≥ 1 normal f/u Bx had progression**

➔ **PSA level changes are NOT accurate predictor of progression, annual Bx needed**

- PSA density higher & free PSA lower in progression group BUT significant overlap

→ Patel et al, J Urol '04

- cohort of 88 men with T1-2 PCa
- median f/u 44months
- DRE and PSA q3mos x 1yr, then q6mos & repeat Bx at baseline, 1yr, then q2-3yrs
- progression evaluated by point system based on several parameters:
 - increase in Gleason score
 - bilateral or multifocal disease
 - >4 cores +ve
 - new lesion on DRE/TRUS
 - PSA velocity >0.75ng/mL/yr

- 36% progression at 5yrs, 45% progression at 10yrs } PSA level NOT predictive

- 1st repeat Bx result most important predictor of progression (multivariate analysis)

- definitiv Rx effective } 17 had RP, 13 had RADs, 1 got hormones

→ only 1 had biochemical recurrence (radiation)

→ Klotz et al, J Urol '04

- prospective study of 299 men with \leq Gleason 7 and \leq T2b (all men \geq 70yrs of age)
- median f/u of 55months
- DRE and PSA q3mos x 2yrs, then q6mos & repeat Bx at 18mos
- progression criteria:
 - PSA progression } DT <2yrs and final PSA >8
 - clinical progression } >doubling of DRE lesion, local progression needing TURP, development of ureteral obstruction, or radiologic/clinical evidence of mets
 - histologic progression } Gleason \geq 8 on repeat Bx at 12-18 months
- at 8yrs, overall survival was 85% and disease-specific survival was 99%
- 60% remained on AS } 24% stopped due to progression & 16% due to pt preference
- 58% of RP patients had pT3a-c and 8% had LN +ve disease

What are the recommendations for active surveillance of patients with PCa?

- no consensus
 - } DRE + PSA q3-6months
 - } repeat Bx 1yr from initial Bx
 - } Bx q1-2yrs thereafter

RADICAL PROSTATECTOMY

Why has RP become more common over the last few decades?

- 1) development of anatomic RRP allowing better dissection & lower complication rates
- 2) improved TRUS-guided Bx
- 3) widespread use of PSA screening

What are the main advantages of RP for PCa?

- possibility of cure
- accurate staging from pathology specimen
- treatment failure more readily identified (biochemical failure – PSA >0.4ng/mL)
- improves cancer-specific & overall survival compared to WW (Bill-Axelsson et al, NEJM '05)
- local recurrence post-RP can be potentially cured with salvage RADs

What are the main disadvantages of RP for PCa?

- need for GA
- hospitalization
- high risk of ED, incontinence
- blood loss
- ??? no improved survival if tumour not contained within prostate or poorly performed RP

What are the advantages & disadvantages of the different approaches to RP (vs retropubic)?

	ADVANTAGES	DISADVANTAGES
Perineal	<ul style="list-style-type: none">- shorter OR time- less blood loss- shorter hospital stay- less anastomotic strictures	<ul style="list-style-type: none">- no access for pelvic LND- higher rate of rectal injury- post-op fecal incontinence- more difficult to spare nerves
Laparoscopic	<ul style="list-style-type: none">- less blood loss- better visualization- less post-op pain, narcotic use- shorter stay- earlier return to work- shorter time with catheter	<ul style="list-style-type: none">- technically difficult- higher rate of complications- need to use heat near NVB- hard to control bad bleeding quickly- ?worse incontinence rates- ?higher +ve margin rates
Robotic	<ul style="list-style-type: none">- greater technical ease- less post-op pain, narcotic use- shorter stay- earlier return to work- 3D vision	<ul style="list-style-type: none">- cost- difficult to rapidly control severe bleeding

What are the advantages & disadvantages of the transperitoneal Lap RP (vs extraperitoneal)?

- advantages } facilitates LND
- disadvantages } higher risk of bowel & vascular injury
- } risk of urinary ascites & post-op bowel obstruction

What are the characteristics of an ideal candidate for RP?

- healthy
 - life expectancy >10yrs
 - biologically significant tumour
 - completely resectable tumour } pre-op clinical & pathologic parameters used to predict pathologic stage (eg Kattan nomogram, Partin tables, etc)
- ➔ **PSA >20, Gleason ≥8 ... pelvic LNs +ve } no benefit of RP ... can abort RadP**

What are the indications to perform a non-nerve sparing RadP?

- 1) high pre-op likelihood of T3 disease (eg Partin)
 - high-volume of disease
 - PSA >10 ng/mL
 - Gleason \geq 8

\ } final decision still reserved
/ until intra-op
- 2) palpable apical lesion
- 3) palpable induration in lateral pelvic fascia
- 4) NVB that is fixed to prostate
- 5) inadequate tissue over surface of prostate after removal (NVB widely excised after the fact)
- 6) pre-op ED or no desire to have sexual function
- 7) pre-op DM, HTN, neurologic diseases, psychiatric diseases } conditions that affect erections

List indications to perform a pelvic LN dissection w/ Rad P (Jason's list ... not from Campbell's)

- depends on risk of LN mets } Partin tables
- staging information, potential for cure in subset of patients, may direct aggressiveness of adjuvant Rx
- 1) T1c disease } PSA >10 + Gleason score \geq 7 (4+3) \
- 2) T2 disease } PSA >10 + Gleason score 7 (3+4) } arbitrary number of ~10% risk of LN mets
- } any PSA + Gleason score \geq 7 (4+3) / as per Partin tables

What are the main steps of a RP?

- pelvic LND (optional)
 - obturator nerve, node of Cloquet, Cooper's ligament, bifurcation of common iliacs
- opening of the endopelvic fascia + limited incision of puboprostatic ligaments
- ligature on superficial dorsal veins (back-bleeding stitch)
- suture ligation and transection of Santorini's dorsal venous complex
- dissection of the urethra at the apex of the prostate and transection of the urethra
- dissection of prostate from NVB
- securing and transection of prostatic pedicles
- dissection of prostate off rectum posteriorly
- transection and reconstruction of BN
- dissection of SVs and ampullary vas
- performance of vesicourethral anastomosis
- placement of JP drain

How long is the post-op Foley left in?

- can be removed 3-21 days after RP
 - depends on how watertight vesicourethral anastomosis is & amount of tension on anastomosis
- removal in <7days associated with 15-20% AUR rate

What is the prognosis after biochemical recurrence post-RP?

- Pound et al JAMA '99
 - 1997 men post-RP (Walsh) } 15% biochemical recurrence (median time = 2yrs)
 - 8yrs from biochemical recurrence to soft tissue mets
 - 2 more yrs until bone mets
 - 2 more yrs until HRPc
 - 12-18months until death

\ } time to death after mets is ~5yrs
/
 - biochemical recurrence precedes cancer-specific mortality by 13 – 13.5yrs
 - time to development of mets predicted by:
 - a) time to biochemical recurrence (> vs \leq 2yrs)
 - b) Gleason score (5-7 vs 8-10)
 - c) PSA doubling time (\geq vs <10months)
 - time from RP to appearance of mets predictive of time until death

What are the predictors of progression of PCa after RP?

- 1) clinical
 - **clinical stage**
 - **Gleason score**
 - **pre-op PSA (total and DT)**
 - 2) pathologic
 - **+ve margins (~50% risk of recurrence)**
 - perineural or lymphovascular invasion
 - **pathologic stage** } non-organ-confined disease
 - } extra-capsular disease (pT3)
 - } SV invasion
 - } LN mets
- pathologic stage is single most powerful prognostic factor**

What is the role of NEOADJUVANT ADT prior to RP?

- nonrandomized studies have shown **lower +ve margin rates** & trends toward improved biochemical outcome } clinical downstaging in 30-90% BUT **pathologic downstaging much less common (8-31%)**
- randomized, prospective trials show **NO BENEFIT of neoadjuvant ADT prior to RP**
- **should mainly be used to decrease size of prostate gland** } ?makes RP technically easier (less blood loss)
- no significant decrease in SV invasion or LN mets
- no improvement in PCa-specific survival or overall survival
- Soloway et al, J Urol '02 \ - RP + 3 months neoadjuvant ADT vs RP alone
- Klotz et al, J Urol '03 } - no significant difference in biochemical recurrence rate
- Aus et al, BJU Int '02 /
- Gleave et al, J Urol '03 } 8 vs 3 months neoadjuvant ADT
- } may improve +ve margin rates
- } no significant difference in biochemical recurrence rate at 3yr interim analysis

How successful is RP for PCa?

- depends on pathology
- **10yr cancer progression-free survival rates (added 5% in each stage in PSA era):**
 - **90% for organ-confined disease**
 - **70% for T3 and -ve margins**
 - **60% for T3 and +ve margins**
 - **30% for SV invasion**
 - **15% for +ve LNs**
- **RP vs WW (Bill-Axelsson NEJM 2005)**
 - 695 men } randomized, prospective
 - mean f/u was 8.2yrs
 - RP reduced disease-specific mortality (RR 0.56) } small absolute reduction (~5%)
 - RP reduced risk of mets (RR 0.6)
 - RP reduced risk of local progression (RR 0.33)
- **RP vs RADS vs WW (Lu-Yao Lancet 1997)**
 - 59, 876 men (SEER database) } retrospective, cohort study
 - overall survival benefit of RP
 - RP better than RADs & WW for all grades of PCa
 - RP especially better than RADs for high grade PCa
 - RP & RADs clearly better than WW for high grade PCa } benefits seen even 5yrs out
 - *** defense } old form of RADs so not comparable ***

What are the main complications following RP?

- **overall complication rate <10%**
- intra-op
 - bleeding (most common)
 - rectal injury
 - vascular injury
 - urethral injury
 - ureteral injury
 - obturator nerve injury
 - MI
 - PE
- post-op (early)
 - urine leak
 - hemorrhage
 - UTI
 - ileus, bowel obstruction
 - wound infection
 - MI/CVA
 - pneumonia
 - DVT/PE (most common cause of mortality)
- post-op (late)
 - ED
 - incontinence
 - inguinal hernia
 - lymphocele
 - BN strictures

How common is urinary incontinence after RP?

- in experienced hands:
 - 90% dry at 1yr
 - depends on age } >95% of men <50yrs and 85% of men >70yrs
 - 1-2% need AUS or sling

What are the RFs for post-RP urinary incontinence?

- patient factors } **patient age**
 - } **pre-op voiding function**
 - } abN detrusor contractility
 - } prior TURP (controversial)
- disease factors } **pre-op or post-op RADs**
 - } **surgical technique (NS vs non-NS)**
 - } higher stage
 - } excessive blood loss
- other factors } surgeon experience

How common is ED after RP?

- depends on age, pre-op potency, NS vs non-NS, comorbidities, surgeon, etc
- in experienced hands:
 - 95% in their 40s, 85% in their 50s, 75% in their 60s, 50% in their 70s if totally normal prior to RP
- erections return starting 3-6 months post-RP and can continue to improve for up to 3yrs

What are the RFs for post-RP ED?

- 1) age >50
- 2) pre-op ED
- 3) extent of nerve-sparing
- 4) surgeon experience
- 5) year of RP

What are the RFs for BN contractures post-RP?

- large blood loss
- urine leak
- previous TURP

What are the most common sites of +ve margins after RadP?

- 1) apex
- 2) posterior
- 3) posterolateral

List 5 technical aspects to repairing a rectal laceration during RadP?

- 1) freshen edges and close in 2 layers with absorbable sutures (gen sx closes rectum in 1 layer only)
- 2) interpose omentum
- 3) copiously irrigate wound with ABx solution
- 4) dilate anus (questionable)
- 5) drain

What are the indications for a diverting colostomy after a rectal injury during a RP?

- end colostomy
- 1) large rectal defect ($\geq 1.5\text{cm}$)
 - 2) hx of pelvic RADs
 - 3) gross spillage of stool
 - 4) hx of long term steroids pre-op

RADIATION THERAPY

External Beam

What is EBRT?

- delivery of beams of gamma radiation (usually photons)
- 3D conformal radiotherapy (3D-CRT)
 - computer alters radiation beams to focus it on prostate gland
 - Heavy particle therapy is another form of 3D-CRT that allows for high doses of radiation
 - beams of high-energy photons 'stopped' w/in tissue to deliver higher doses
 - intensity-modulated radiation therapy (IMRT) is the most sophisticated form of 3D-CRT
 - localizes radiation dose to geometrically complex fields with least collateral damage
- *** the more localized you get, the more prostate movement affects therapeutic effect ***

What doses of radiation are usually administered for PCa?

- | | | |
|---------------------|------------|--|
| - low risk | } 70-72 Gy | } most now getting minimum 78Gy |
| - intermediate-risk | } 75-76 Gy | |
| - high-risk | } 80+ Gy | |

What are the main side effects of EBRT?

- acute side effects } occur in 1/3 but is self-limited in 90-95%
- proctitis
 - cystitis
- long-term side effects
- ED } 50% usually starting at 1yr post-EBRT (PDE-5 inhibitors work well)
 - incontinence
 - urethral stricture
 - bladder irritability
 - intermittent gross hematuria (radiation cystitis)
 - prostatic-rectal fistulae
 - intermittent rectal bleeding
 - IBS
 - 2nd malignancies

*** **EBRT causes MORE RECTAL toxicity and less urinary toxicity than brachy** ***

What are the contraindications to EBRT for PCa?

- ABSOLUTE
 - previous pelvic RADs
- RELATIVE
 - previous TURP
 - severe LUTS
 - IBD

What pre-treatment factors predict recurrence (clinical & biochemical) post-EBRT?

- 1) PSA level
- 2) Gleason score
- 3) clinical stage (AJCC '92)
- 4) % of positive Bx cores } also found to predict time to biochemical failure

What post-treatment factors predict recurrence post-EBRT?

- **PSA nadir value } strongest independent RF for failure**
 - absolute threshold unknown but good if $<0.5\text{ng/mL}$
 - nadir $>2\text{ng/mL}$ likely means distant failure
- time to PSA nadir } slower/longer time to nadir better
 - time to failure $<12\text{mos}$ likely means distant failure
- post-nadir PSA DT } associated with type of failure
 - shorter/faster DT ($<3\text{-}6\text{mos}$) likely means distant failure

Table 100-1 -- Failure Pattern According to Level of PSA Nadir, Time to Nadir, and PSA Doubling Time

	PSA Nadir (ng/mL)	Time to Nadir (mo)	PSA Doubling Time
NED	0.4-0.5	22-33	NA
Local failure	1.0-2.0	12-18	11-13 mo
Distant failure	>2.0	<12	3-6 mo

What are the 3 potential sources of PSA that contribute to the nadir post-EBRT?

- 1) residual benign prostatic epithelium
 - lower and longer time to nadir (eg nadir $<0.5\text{ ng/mL}$ with time to nadir $>2\text{yrs}$)
- 2) residual local PCa cells
- 3) subclinical micromets
 - higher and earlier nadir (eg nadir $>2\text{ng/mL}$ with DT $<3\text{ months}$)

What is the definition of biochemical failure after EBRT?

- endpoint difficult to assess because PSA level gradually decreases for up to 2-3yrs after EBRT
- inflammation in prostate can produce transient PSA elevations } PSA bounce
 - } more common with brachy
 - } usually seen during first 2yrs
- 1) **ASTRO } 3 consecutive increases in PSA measured 3-4mos apart if $<2\text{yrs}$ after EBRT or 6months apart if $>2\text{yrs}$ after EBRT**
 - time of progression back-dated to half-way b/w PSA nadir and 1st rise
 - } takes yrs to determine progression
 - time to nadir, then time for 3 rises
 - may make EBRT look better (???controlled by long f/u)
 - back-dating minimizes impact of recurrence on survival curve (larger denominator)
- 2) **Pheonix criteria } PSA rise of 2ng/mL above nadir**
 - back-dating eliminated
 - may make EBRT look even better because of time it takes to rise by 2ng/mg (time to nadir, then time to rise to 2ng/mL)

What is the optimal duration and timing of hormones with EBRT?

- overall survival benefit with longer hormone therapy } especially in high-risk PCa
- Hanks et al J Clin Oncol 2003
 - 4months peri-EBRT hormones then randomized to no further Rx vs 24months more of hormones (ie 28 total vs 4)
 - 28months of hormones better in all clinical endpoints EXCEPT overall survival

What is the role for adjuvant ADT after EBRT for localized PCa?

- much of data extrapolated from BOLLA protocol for locally advanced PCa
- no RCT looking at EBRT + hormones exclusively for high-risk PCa patients w/ localized PCa
- 1) locally advanced PCa } EBRT + hormones x3yrs**
- 2) high-risk (PSA >20, G8-10 or ≥T3), localized PCa } EBRT + hormones x3yrs**
- 3) intermediate-risk (PSA 10-20, G7 or T2b), localized PCa } EBRT + hormones x6mos**
- **Bolla et al, NEJM '97**
 - 401 men with locally advanced PCa } prospective, randomized
 - ~80% of men had T3 disease
 - RADS vs RADS + LHRH (Zoladex x 3yrs)
 - overall survival at 5yrs better for RADS + hormones } 78% vs 62%
 - disease-free survival at 5yrs better for RADS + hormones } 85% vs 48%
 - 5yr local control rate better for RADS + hormones } 97% vs 77%
 - progression rates higher for RADS alone
- **Bolla et al, Lancet '02 (update of NEJM '07)**
 - 412 men with locally advanced PCa
 - randomized to RADS vs RADS + LHRH agonist for 3yrs (Zoladex)
 - median f/u 5.5 yrs
 - significant improvement in overall survival & disease-free survival with adjuvant ADT
 - 5yr overall survival was 78% (vs 62%)
 - 5yr disease-free survival was 74% (vs 40%)
 - 5yr PCa-specific survival was 94% (vs 79%)
- **D'Amico et al JAMA '04**
 - RCT OF 206 men } EBRT + hormones vs EBRT alone for intermediate and high risk PCa patients with localized PCa
 - median f/u of 4.5yrs
 - 6months of Lupron/Zoladex had overall survival benefit at 5yrs (88% vs 78%)
 - improved outcomes seen mainly in intermediate risk group
- ALL THESE STUDIES ARE MISSING "HORMONES ONLY" ARM ... maybe just all hormone effect?"

How successful is EBRT?

- 10yr cure rates for localized PCa are ~50% } lower than RP but this is old EBRT
- better results with 3D-CRT and IMRT } 5yr progression-free rates 70-85%
- intermediate & high-risk pts often given hormones too } is some of survival just a hormone effect???
- brachy + EBRT also used for high-risk patients
- combined androgen blockade better for patients w/ high PSA, high Gleason score, or large-volume PCa
- ~30% of patients receiving EBRT have tumour persistence } usually at central part of tumour

Brachytherapy

What is brachytherapy?

- implantation of radioactive seeds directly in prostate to deliver high-dose radiation
- **iodine-125** or **palladium-103 seeds** } no significant advantages between the two

How much radiation is delivered to the prostate with brachytherapy?

- iodine-125 } 145 Gy
- palladium-103 } 125 Gy

What are the ASTRO criteria for eligibility for brachy?

- PSA <10-15
 - Gleason ≤ 6 (unless part of study or in combo with EBRT)
 - $\leq T2a$
 - volume <50-60g
 - IPSS <7 (mild)
 - Qmax >10cc/sec
- \ } ie D'Amico low-risk group
/ }
- sometimes hormones used to shrink prostate (can affect survival data)

What are the contraindications to brachytherapy for PCa?

- high-volume, high risk PCa } doesn't meet ASTRO criteria for low risk disease
 - } unless part of study (with EBRT boost)
- large prostate (>50g) } pubic arch may interfere with seed placement
 - } sometimes hormones used to shrink prostate (can affect outcomes)
- very small prostate (<20g) } hard to implant seeds
- severe LUTS (IPSS >7 or Qmax <10cc/sec)
- large median lobes
- previous TURP } higher risk of superficial urethral necrosis & seeds don't stay

How successful is brachytherapy?

- excellent short-term cancer control rates } especially for Gleason 6
- 7yr progression-free survival rates are ~80% (ASTRO criteria)

What are the main side effects of brachytherapy?

- ED } less common cf EBRT
 - } occurs in 20-40%, higher if combined with EBRT
 - } takes a while to develop (~1-2yrs)
- urinary incontinence
- AUR } 20-25% (seems too high!!! ... 1-5% on RADs chapter)
 - } ~10% need a TURP after brachy (high rate of incontinence if too aggressive)
- bladder irritation
- urethral stricture
- proctitis } less common than EBRT
- rectourethral fistula
- seed migration

*** **Brachy causes more URINARY toxicity and less rectal toxicity than EBRT** ***
→ most patients given pre-op α -blockers and hormones

Which patients are at increased risk of complications post-brachy?

- prior EBRT
- prior TURP
- seeds closer than 7mm to rectum
- seeds close to urethra
- severe LUTS (high IPSS)
- hx of prostatitis
- prostate size >60g

How is brachy combined with EBRT?

- brachy used as a boost before or after EBRT } pts generally have higher stage disease
- **45 Gy EBRT dose + brachy boost 60-70% of regular implantation dose**
- 5yr biochemical-recurrence free survival from 90-95%
- 10yr biochemical-recurrence free survival 70-75%

Adjuvant Radiation

What is the role of adjuvant RADS after RP?

- main indication is for adverse findings on RP pathology → +ve margins
→ SV invasion
→ T3 disease
- usually **60-64 Gy to prostate bed** } advisable to wait 3-4 months after RP
- no improvement in overall survival has been demonstrated } emerging data shows benefit!!!!
- **Bolla et al, Lancet 2005 (EORTC)**
 - 1005 men randomized to adjuvant RADS vs surveillance
 - pT3, SV invasion, +ve margin
 - **improved biochemical progression-free survival & local progression**
 - **NO OVERALL SURVIVAL BENEFIT**
- **Thompson et al, JAMA '06 (SWOG)**
 - 425 men randomized to adjuvant RADS vs surveillance
 - pT3, SV invasion, +ve margin
 - improved PSA relapse rate & disease recurrence rate
 - TREND towards improved mets-free & overall survival } **update shows benefit !!!**

What are the criticisms against adjuvant RADS post-RP?

- 1) not all patients with pT3 or +ve margins have local tumour recurrence
 - overtreatment with RADS } overtreatment in 20% for pT3 and 50% for +ve margins
 - may recur with distant mets not locally
- 2) no evidence to suggest adjuvant post-RP RADS is any better than early salvage RADS
 - adjuvant always look better due to bias (includes Rx of those that will never recur)

What are the side effects of adjuvant radiation therapy?

- 5-10% risk of radiation proctitis
- 50% chance of ED
- will likely worsen any post-RP urinary incontinence but usually doesn't induce new UI

Radiation vs RP

Why is it difficult to compare EBRT to RP?

- endpoints used for treatment failure are different
 - undetectable PSA vs ASTRO/Phoenix criteria
- PSA often doesn't reach recommended nadir of 0.2 ng/mL in EBRT group
- EBRT often given with hormones

What evidence suggests RP is better than EBRT for localized PCa?

- **Lu-Yao et al, Lancet 1997**
 - 60 000 men from SEER database
 - population based, retrospective study
 - RP better than EBRT and WW
 - RP especially better for high grade PCa
- caveat } old EBRT technology, so less RADS given due to increased S/E profile

BIOCHEMICAL RECURRENCE

When does biochemical recurrence usually occur after RP?

- 50% within 3yrs
 - 80% within 5yrs
 - 99% occur within 10yrs
- \ } rare to see recurrence after 15yrs
/

What predicts the progression of PCa after biochemical recurrence?

- 1) PSA velocity or PSA DT
 - 2) time from RP to biochemical recurrence
 - 3) Gleason score
- **Pound et al, JAMA '99** } retrospective review of Walsh's RP data
 } 1997 men with mean time to PSA failure of 2yrs
 } mean time to mets after biochemical failure is 8yrs
 - only 34% overall actually developed clinical mets
 } mean time to death after mets is 5yrs
 } mean time to death after biochemical failure is 13yrs

What are the features suggestive of distant mets after RP, rather than local recurrence?

- 1) PSA that never nadirs to undetectable } >2ng/mL predictive of distant mets
- 2) short interval of undetectable PSA } <1yr before biochemical recurrence
- 3) rapidly rising PSA after biochemical recurrence } PSA DT <3-6 months
 } PSA velocity >0.75 ng/mL
- 4) -ve surgical margins
- 5) T3 disease or +ve SVs or +ve LNs
- 6) higher Gleason score

When is the best time for salvage RADs for biochemical recurrence post-RP?

- Bolla et al '05 showed early adjuvant RADs for +ve SVs, +ve margins, or pT3a disease
- but no RCT evidence of survival benefit for early RADs over salvage RADs
- Cox et al, J Clin Onc '99 (ASTRO consensus statement) \ now considered much earlier
- recommends trigger before 1.5 ng/mL / (eg 0.5 ng/mL)

What are the factors predictive of a good response to salvage RADs post-RP?

- 1) long interval of undetectable PSA before biochemical recurrence (>2yrs)
- 2) PSA DT >10months
- 3) pre-salvage RADs PSA <2ng/mL
- 4) no LN mets
- 5) +ve margins } if margins +ve, may respond better to salvage RADs
- 6) no SV invasion
- 7) low-grade PCa

How successful is salvage RADs post-RP?

- Stephenson et al, JAMA '04
 - 501 men with recurrence post-RP
 - 56% had pT3a, 28% had pT3b
 - 3% had N+ disease
 - median pre-salvage RADS PSA = 0.72 ng/mL
 - 50% had disease progression at median f/u of 45months after salvage RADS
 - 10% developed mets at 45months
 - 4% died of PCa at 45months
 - 45% were progression-free at 4yrs

What are the predictors of progression post-salvage RADs?

- Stephenson et al, JAMA '04 }
 - 1) Gleason ≥ 8
 - 2) PSA DT <10 months
 - 3) -ve margins
 - 4) + SV involvement
 - 5) pre-salvage RADs PSA >2ng/mL

When is the appropriate time to initiate ADT for biochemical failure post-RP?

→ UNKNOWN

- early hormones better than delayed hormones if N1 PCa (Messing et al, Lancet '97)
 - improvement in overall survival (HR 1.84)
 - improvement in PCa-specific survival (HR 4.09)
 - improvement in progression-free survival (HR 3.42)

\ } some flaws of study though
/ }
- no difference in early clinical outcomes between early & delayed hormone Rx in men with biochemical failure post-RP (Moul et al, J Urol '04)
 - retrospective, observational analysis of 1352 men } early vs late ADT
 - early therapy only beneficial for high-risk PCa group (decreased time to bone mets)
- delayed or intermittent hormone therapy often used to avoid side effects of hormone Rx
 - especially a slowly rising PSA level
 - no strong evidence that intermittent therapy is better than continued therapy
 - balance between survival outcomes and adverse effects of androgen blockade

What is the ideal timing of ADT in all-comers?

1) low-risk, localized PCa

→ no overall survival benefit to immediate ADT

→ they likely do worse (toxicity of hormones)

- 2) locally advanced, asymptomatic mets, & clinically present but undefined PCa
 - immediate ADT results in significantly better PCa-specific survival BUT NOT overall survival
- 3) in N+ disease without primary treatment
 - there is no significant advantage to immediate ADT
 - 1.6yr median survival advantage vs 1.8yrs more on ADT
- 4) in N+ disease after RP, there is a significant survival advantage to immediate ADT
 - 2.6yr difference in median overall survival

What are the main options for local recurrence after RADs?

- 1) WW
- 2) cryotherapy
- 3) hormones
- 4) salvage prostatectomy

What are the eligibility criteria for salvage RadP?

- patient with excellent health and life expectancy >15yrs
- no evidence of mets
- at initial presentation (before RADs) had unequivocally clinically localized PCa
- TRUS Bx, Gleason grade, DRE, serum PSA levels, etc all suggest localized disease

What are the predictors of progression after salvage Rad P?

- Bianco et al, Int J Rad Oncol Biol Phys '05
 - 1) pre-op PSA >10
 - 2) SV invasion
 - 3) +LN mets

What are the complications of salvage RadP?

- significantly improved in modern era
- rectal injury slightly more common (~5%) } if good bowel prep & small injury, primary repair possible
- urinary incontinence rates are still high } ~50% are incontinent (even higher after brachy)
 - } ~**20% need AUS (cf 1-2% after RadP)**
 - } ~30% develop an anastomotic stricture
- almost all get ED
- +ve margin rates higher
- hemorrhage more common
- fistula rate higher
- wound infections more common

OTHER TREATMENTS

What other treatment options are available for localized PCa?

→ **RP, EBRT, Brachy are mainstay and should be offered to all**

- 1) primary hormone therapy
 - mainly for older men with significant comorbidities
 - NOT CURATIVE but many men get long-term remission
 - LHRH analogs have largely replaced orchiectomy and estrogen
 - anti-androgens have less sexual & bony side effects but more CVS side effects
- 2) cryoablation
 - **argon gas to freeze prostate while helium gas warms the urethra**
 - has been tried as salvage post-RP & post-RADs
 - PSA rises to very high levels immediately after cryo then nadirs by 3 months
 - decent results with improving complication rate
 - AUR, SUI, urinary-bowel fistula, strictures, chronic rectal/perineal pain, **ED (>80%)**
 - **no long term cancer control & QOL outcomes data available**
 - what defines failure
 - many get hormones
- 3) HIFU
 - **focused acoustic energy used to heat (up to 100C) and thus ablate focal lesions or the entire gland (done under GA or spinal)**
 - ablatherm vs sonablate
 - Sonablate can treat larger prostates (Can-Am) cf ablatherm (US HIFU)
 - produces sharp, predictable lesions of ablation
 - requires days to months for necrosis & cavitation to occur
 - treatment can be repeated
 - not recommended for glands >40g } sometimes a limited TURP or TUIBN done before to reduce risk of AUR
 - } **AUR most common side effect (~20%)**
 - } most patients need S/P tube temporarily
 - potential complications include AUR, urinary fistula, incontinence, urethral stricture, perineal pain, ED (30-60%)
 - only 70% progression-free survival with mean f/u of 23months
 - mainly low or intermediate risk so outcomes are not that great
 - has been used as 1° treatment and for radiation failures
 - **no long term data to support HIFU as standard therapy**
- 4) RF Interstitial Tumour Ablation
 - office-based hyperthermia of prostate (lower temps) that supposedly kills PCa cells selectively
 - has been tried as 1° treatment in combination with RADs and for salvage post-RADs
 - **no long term cancer control & complications data available**

RECOMMENDATIONS FOR TREATMENT BY PATIENT RISK GROUPS

What are the defined risk groups for PCa?

- 1) Low-risk
 - T1a or T1c
 - PSA <10
 - Gleason ≤6
 - unilateral or <50% of core involved
- 2) Intermediate-risk
 - T1b or T2a
 - PSA <10
 - Gleason 6 or 7 (3+4)
 - bilateral cores involved
- 3) High-risk
 - T2b or T3
 - PSA 10-20
 - Gleason 7 (4+3)
 - >50% of cores involved or perineural invasion or ductal differentiation
- 4) Very high-risk
 - T4
 - PSA >20
 - Gleason ≥8
 - lymphovascular invasion or neuroendocrine differentiation

What are the different risk groups for PCa based on pretreatment clinical parameters?

→ D'Amico et al '01 (MSK)

- low-risk } ≤T2a, PSA ≤10, AND Gleason ≤6
→ disease-free survival at 10yrs post-RP = 83%
- intermediate-risk } T2b OR PSA 10-20 OR Gleason 7
→ disease-free survival at 10yrs post-RP = 46%
- high-risk } ≥T2c OR PSA >20 OR Gleason ≥8
→ disease-free survival at 10yrs post-RP = 29%

What are the treatment recommendations for each risk group based on life expectancy?

	0-5 yrs	5-10yrs	>10yrs
Low risk	- AS - hormones	- AS - Rads - hormones - other	- RP - Rads - AS - other
Intermediate Risk	- AS - hormones - Rads - other	- Rads - hormones - RP - other	- RP - Rads - other - hormones
High risk	- AS - Rads - other	- Rads - hormones - RP - other	- Rads - RP + Rads + hormones - hormones
Very high risk	- AS - Rads - other	- hormones - Rads + hormones - systemic Rx	- Rads + hormones - RP + Rads + hormones - hormones - systemic Rx - investigational Rx

*** if >20% chance of +ve LNs then options are WW, hormones, systemic Rx + hormones ***

→ PSA >20ng/mL has ~20% chance of +ve LN mets

Chapter #96 – WW and Active Surveillance

WATCHFUL WAITING VS ACTIVE SURVEILLANCE

How common is PCa?

- most common visceral malignancy in men
- 3rd highest cause of cancer-related death in Canada (lung, colon) } 2nd in US
- peak incidence between ages of 70-74 } 85% diagnosed after age 65yrs
- lifetime risk is 1 in 6 (~17%) for caucasians (1 in 5 for Blacks)
- lifetime risk of death from PCa is 1 in 36 (~3%) for Caucasians (1 in 21 for Blacks)
- incidence of PCa rose sharply in early 90's after introduction of PSA in 1987
- incidence then fell sharply until 1995 ("cull effect") and now has been rising slowly
- mortality rate has been declining since early 90's

What is the difference between WW and active surveillance?

- WW } no treatment except for palliation of symptoms
 - goal is to limit morbidity from disease and therapy
- AS } delay of curative treatment until evidence of progression
 - goal is to distinguish clinically insignificant cancers from life-threatening ones while they are still localized
 - avoiding overtreatment while administering curative therapy to select cases

Table 96-2 -- Contrasts Between Active Surveillance and Watchful Waiting (Parker, 2004)

	Active Surveillance	Watchful Waiting
Aim	To individualize treatment	To avoid treatment
Patient characteristics	Fit for radical treatment	Age > 70 yr or life expectancy < 15yr
	Age 50-80 yr	
Tumor characteristics	T1-T2, GS ≤ 7, initial PSA < 15 ng/mL	Any T stage, GS ≤ 7, any PSA
Monitoring	Frequent PSA testing	PSA testing unimportant
	Repeated biopsies	No repeated biopsies
Indications for treatment	Short PSADT	
	Higher grade or more extensive cancer on biopsy	Symptomatic progression
Treatment timing	Early	Delayed
Treatment intent	Radical	Palliative

WATCHFUL WAITING VS TREATMENT

What evidence exists for WW?

- **most early stage PCa patients have an indolent course for 10-15yrs**
- **substantial increase in local tumour progression & aggressive mets after 10-15yrs**
- overall survival **depends strongly on stage & grade**, as well as age of patient
- Chodak et al, NEJM '94
 - 828 men from 6 different non-randomized studies
 - WW + delayed hormones } no RP, no RADs
 - 10yr mortality for low-grade PCa was only 13% but 66% for high-grade PCa
 - 10yr risk of mets depends on Gleason grade } 19% for low-grade, 42% intermediate-grade, 74% high-grade
- Johansson et al, JAMA '04
 - population-based cohort study
 - 223 men with ≤clinical T2 PCa diagnosed on TURP or DRE } non-screened men
 - most cancers have indolent course during first 10-15yrs
 - progression-free survival, mets-free survival, PCa-specific survival much worse b/w 15 to 20yrs
 - only high-grade PCa group had excess PCa-related mortality earlier on
 - grade was strongest predictor of survival on multivariate analysis
- Albertsen et al, JAMA '05
 - retrospective population-based, cohort study
 - 767 men between ages 55 to 74yrs with ≤clinical T2 PCa
 - observation OR hormones (immediate or delayed)
 - men with low-grade PCa have minimal risk of death from PCa during 20yrs of f/u
 - men with high-grade PCa have high risk of death within 10yrs

What evidence exists that RP makes a difference?

- Bill-Axelsson et al, NEJM '05
 - Scandinavian Trial with 695 men with clinically localized PCa } **unscreened men**
 - randomized to RP or WW (with systemic Rx once symptomatic progression)
 - primary endpoint was death from PCa } median f/u was 8.2yrs
 - 50 deaths in WW arm vs 30 deaths in RP arm (relative HR of 0.56)
 - RP arm had lower relative risk of distant mets (relative HR 0.60)
- Lu-Yao et al, Lancet '97
 - ~60,000 men from SEER database with PCa
 - 10yr PCa-specific survival was higher for RP than WW or RADs } esp for high grade

Which men are good candidates for WW?

- low risk PCa + life expectancy of <20yrs
- intermediate risk PCa + life expectancy of <10yrs
- high-risk PCa + life expectancy of <5yrs

IDENTIFYING MEN WITH “LOW-RISK” PROSTATE CANCER

What is the Epstein definition of a clinically “insignificant” tumour?

- organ-confined tumour <0.2mL
- Gleason ≤ 6

What is the Epstein criteria for low-risk (“insignificant”) PCa?

- 1) Gleason ≤ 6
 - 2) PSA density <0.15ng/mL
 - 3) ≤ 2 needle cores +ve (minimum 6 total cores)
 - 4) <50% in any +ve core
 - 5) f/t ratio ≥ 0.15
- } ADDED in 1998
- } → ~16% of men in original series ('94) had “insignificant” PCa
/ → 94% PPV for insignificant PCa

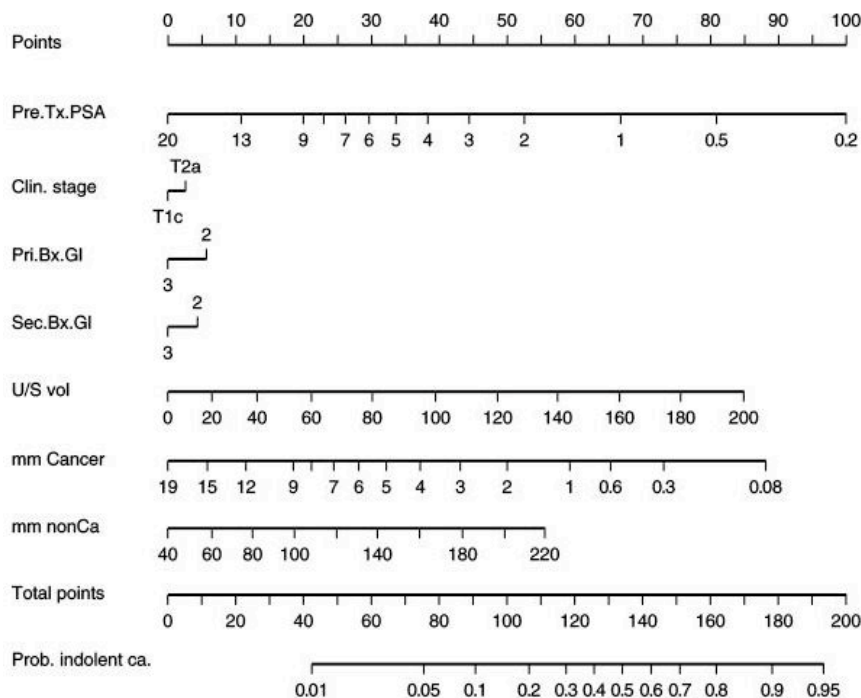
What is the Kattan definition for indolent PCa?

- organ confined tumour <0.5mL
- Gleason ≤ 6

What are the Kattan nomograms for indolent PCa?

→ **statistical model used to predict presence of indolent PCa** (Kattan et al, J Urol '03)

- based on >400 men who underwent RP } 20% of low-risk PCa group had “indolent disease”
- point system from 0 to 200 and includes **7 variables** } **higher score = indolent PCa**
 - 1) pre-treatment PSA
 - 2) clinical stage
 - 3) primary Gleason score
 - 4) secondary Gleason score
 - 5) U/S volume of prostate
 - 6) mm of cancer
 - 7) mm of non-cancer



→ KATTAN NOMOGRAM

ACTIVE SURVEILLANCE

What evidence exists that active surveillance is safe?

→ **no great RCTs**

→ **Carter et al, J Urol '02 (Walsh/Epstein)**

- cohort of 81 men with stage T1c PCa (Epstein criteria)
- median f/u of 23 months
- DRE and PSA q6mos & repeat Bx q1yr
- progression defined based on f/u Bx:
 - Gleason 4 or 5
 - ≥ 3 cores +ve
 - $>50\%$ involvement of a core
- **31% progression } 56% had progression if every f/u Bx showed PCa**
} only 7% of men with ≥ 1 normal f/u Bx had progression
- **PSA level changes are NOT accurate predictor of progression, annual Bx needed**
 - PSA density higher & free PSA lower in progression group BUT significant overlap

→ **Patel et al, J Urol '04**

- cohort of 88 men with T1-2 PCa
- median f/u 44months
- DRE and PSA q3mos x 1yr, then q6mos & repeat Bx at baseline, 1yr, then q2-3yrs
- progression evaluated by point system based on several parameters:
 - increase in Gleason score
 - bilateral or multifocal disease
 - >4 cores +ve
 - new lesion on DRE/TRUS
 - PSA velocity $>0.75\text{ng/mL/yr}$
- **36% progression at 5yrs, 45% progression at 10yrs } PSA level NOT predictive**
- **1st repeat Bx result most important predictor of progression (multivariate analysis)**
- definitive Rx effective } 17 had RP, 13 had RADs, 1 got hormones
 - only 1 had biochemical recurrence (radiation)

→ **Klotz et al, J Urol '04**

- prospective study of 299 men with \leq Gleason 7 and \leq T2b (all men ≥ 70 yrs of age)
- median f/u of 55months
- DRE and PSA q3mos x 2yrs, then q6mos & repeat Bx at 18mos
- progression criteria:
 - PSA progression } DT <2 yrs and final PSA >8
 - clinical progression } $>$ doubling of DRE lesion, local progression needing TURP, development of ureteral obstruction, or radiologic/clinical evidence of mets
 - histologic progression } Gleason ≥ 8 on repeat Bx at 12-18 months
- at 8yrs, overall survival was 85% and disease-specific survival was 99%
- **60% remained on AS } 12% stopped d.t. progression & 16% due to pt preference**
- **58% of RP patients had pT3a-c and 8% had LN +ve disease**

What is the goal of active surveillance?

- **avoiding unnecessary Rx** (and associated morbidity) of men with indolent, low-risk PCa while also **avoiding the progression of a curable cancer** to metastatic disease
- **delaying curative therapy** for low-risk PCa that shows evidence of progression
- initial evaluation before AS aims to reduce the chance that a large, aggressive cancer is missed while surveillance aims to detect progression before development of mets

What is the recommended surveillance schedule at MSK?

- complete re-evaluation at baseline presentation
 - DRE
 - free and total PSA
 - imaging of the prostate (endorectal MRI with spectroscopy)
 - TRUS Bx
- DRE and PSA q6months
- repeat imaging and TRUS Bx 12-18 months after baseline evaluation
- repeat imaging and TRUS Bx q2-3yrs

What are the main triggers for recommending definitive therapy?

- increased Gleason grade on Bx
- increased cancer volume on Bx
- patient anxiety

What are the predictors of progression of PCa?

- 1) **repeat TRUS Bx** } good predictor of cancer progression
 - } abN repeat Bx associated with ~40% 5yr progression-free probability
 - VS ~80% if repeat Bx is normal
- 2) **PSA DT** } decent predictor of cancer progression
 - } BUT, exact trigger point at which to recommend treatment uncertain (? <2yrs)
- 3) DRE } not a good predictor of progression
 - } however, important as an indicator that a repeat Bx is warranted
- 4) serial imaging (TRUS, CT, MRI) } limited value

Chapter #97 – Radical Retropubic Prostatectomy

SURGICAL ANATOMY

What is the arterial blood supply to the prostate?

- **inferior vesical artery** } gives off branches to base of bladder, SVs, and prostate
 - } terminates into 2 large groups of prostatic vessels
 - urethral group } supply BN and periurethral portion of gland
 - capsular group } runs with NVB and supplies prostatic capsule

What is the venous drainage of the prostate and surrounding tissues?

- **venous drainage is through Santorini's plexus**
- deep dorsal veins } leave penis under Buck's fascia between corpora cavernosa and then penetrates UG diaphragm, dividing into 3 major branches
 - **superficial branch** } travels between puboprostatics & overlies BN and prostate
 - R lateral venous plexus \ travels within prostatic fascia and
 - L lateral venous plexus / traverses posterolaterally, communicating freely with branches of the internal iliac
- **lateral plexus** drains into pudendal, obturator, and vesical plexuses
 - also gives off branches into levators

What is the blood supply to the penis?

- internal pudendal artery } terminal branch is common penile artery (dorsal, cavernosal, and bulbourethral branches given off)
- aberrant supply from obturator, inferior & superior vesical also exist } divided during RP

What is the nerve supply to the pelvic organs & genitals?

- pelvic plexus } has parasympathetic efferent pre-ganglionic fibers via pelvic nerve (S2-S4)
 - } also has sympathetics from thoracolumbar plexus via hypogastric nerve (T10-L2)
- cavernous nerves } travel outside prostatic capsule in lateral pelvic fascia b/w prostate & rectum (NVB)
 - } pierce UG diaphragm and travel behind dorsal penile nerve before entering corpora cavernosa

Describe the membranous urethra and the EUS?

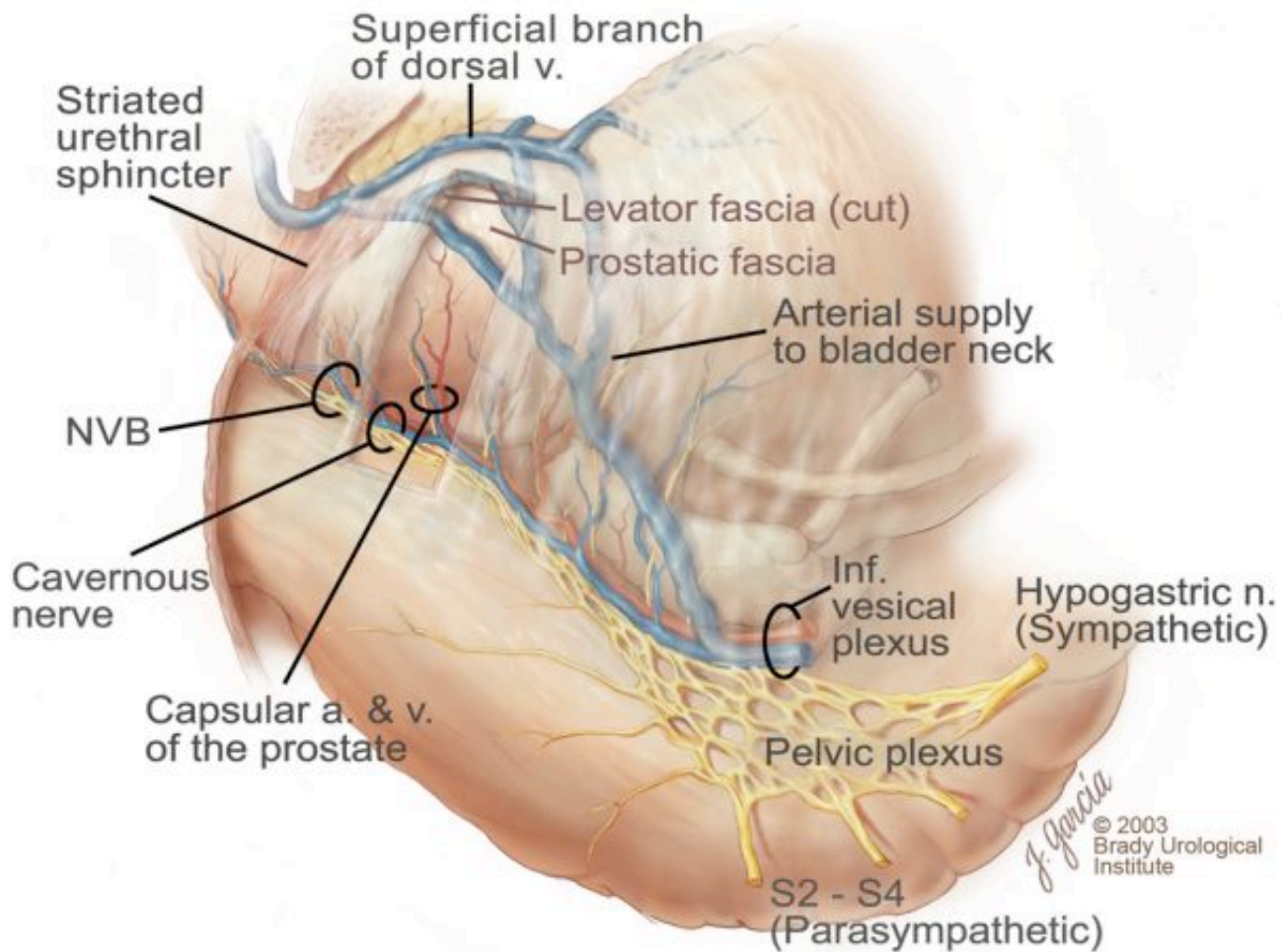
- covered by EUS → distally forms omega shape as it fans out laterally over perineal membrane
 - innervated by the **pudendal nerve (somatics)** & a **branch of the sacral plexus (parasympathetics)** that runs on the surface of the levators
- membranous urethra is 'suspended' from the pubis by connective tissue that inserts into puboprostatic ligament and suspensory ligament of the penis

Which muscles provide urinary continence after RP?

- 1) striated sphincter } fatigue-resistant, slow-twitch fibers (passive control)
- 2) rhabdosphincter/levator ani } somatically innervated muscle (active control)
- both are supplied mainly by pudendal nerve

What are the 3 fascial layers covering the prostate?

- 1) Denonvilliers' fascia } between anterior wall of rectum and prostate
- 2) prostatic fascia } in direct continuity with "capsule" of prostate anteriorly & anterolaterally
→ major tributaries of dorsal vein of penis & Santorini's plexus travel within anterior prostatic fascia
- 3) levator fascia } fuses with prostatic fascia laterally
→ prostate gets blood supply and autonomic innervation b/w layers of levator and prostatic fascia



SURGICAL TECHNIQUE

What are the main points of a Radical Retropubic Prostatectomy (Walsh)?

- patient supine, flat } maintain relative hypoTN w/ minimal hydration until prostate removed
- lower midline incision (pubis to halfway to umbilicus) used to develop space of Retzius
- mobilize peritoneum off external iliac vessels, preserving soft tissue overlying vessels, which contain lymphatics } vas deferens is NOT divided
- lymphadenectomy performed before RadP when indicated } palpable abN or Gleason ≥ 8
- defat prostate to expose endopelvic fascia, puboprostatics & superficial branch of dorsal vein
- endopelvic fascia entered laterally away from bladder & prostate
- levators swept off lateral aspect of prostate } small pudendal perforators ligated with clips
- puboprostatic ligaments divided } pubourethral component of DVC preserved to maintain anterior fixation of striated urethral sphincter to pubis
- accessory pudendal vessels preserved for erectile function
- 3-0 monocryl suture passed superficially through DVC and tied to perichondrium of pubic symphysis
 - } controls venous bleeding without "bunching" effect
 - } recapitulation of puboprostatics to add support to striated sphincter
 - } fixation of DVC distally
- suture left to oversee bleeders once DVC is cut
- 2-0 chromic back-bleeding stitch placed near BN
- DVC cut with Metzenbaums under direct vision
 - can perform early, high bundle released through levator fascia before cutting DVC
- DVC suture used to oversee striated urethral sphincter & DVC (running suture)
- proximal dorsal vein is oversewn also in the shape of a V (running suture)
- lateral bands of striated muscle released from urethra
- Lauer clamp passed under urethra and anterior 2/3 of urethra is transected close to apex
- 5 urethral sutures placed initially } take bite of mucosa + submucosa, but not smooth muscle
- 6 o'clock suture placed and then posterior urethra is transected after removal of catheter
- urethral plate divided posteriorly very carefully
 - to obtain good margins for apical lesions
 - identifying correct plane on anter. rectal wall ensures excision of Denonvillier's fascia
 - avoids blunt trauma to NVB
 - helps to preserve urinary continence
- release of lateral pelvic fascia } composed of levator fascia & prostatic fascia
 - NVB found between these layers
- release of NVB from posterolateral aspect of prostate as prostate is rolled up off rectum
 - NVB widely excised with prostate if non-nerve sparing RadP indicated
- divide Denonvillier's fascia to expose SVs and ampulla of vas } can divide these now or later
- BN incised and prostate removed
- BN reconstructed in tennis racket fashion then mucosa is everted with 4-0 sutures
- intussusception of BN w/ 2-0 suture then vesicourethral anastomosis tied down over 16Fr Foley
 - anterior sutures tied first
- JP drain placed

What are the advantages of regional anesthesia (epidural) for a RadP?

- less blood loss
- lower frequency of PE

How long after Dx should RadP be deferred?

- TRUS Bx } wait 6-8 wks
- TURP } wait 12 wks

What are the limits of the standard pelvic lymphadenectomy done for a RadP?

- anterolaterally } external iliac artery
- posteriorly } obturator nerve → some dissect and take obturator nodes also
- inferiorly } node of Cloquet
- superiorly } bifurcation of common iliacs

What are the most common sites of +ve margins after RadP?

- 1) apex
- 2) posterior
- 3) posterolateral

What are the indications to perform a non-nerve sparing RadP?

- 1) high pre-op likelihood of T3 disease (eg Partin)
 - high-volume of disease \
 - PSA >10 ng/mL } final decision still reserved
 - Gleason ≥8 / until intra-op
- 2) palpable apical lesion
- 3) palpable induration in lateral pelvic fascia
- 4) NVB that is fixed to prostate
- 5) inadequate tissue over surface of prostate after removal (NVB widely excised after the fact)
- 6) pre-op ED or no desire to have sexual function
- 7) pre-op DM, HTN, neurologic diseases, psychiatric diseases } conditions that affect erections

COMPLICATIONS

What are the main complications following RP?

- **overall complication rate <10%**
- intra-op
 - bleeding (most common)
 - rectal injury
 - vascular injury
 - urethral injury
 - obturator nerve injury
 - ureteral injury
 - MI/PE/etc
- post-op (early)
 - urine leak
 - hemorrhage
 - UTI
 - ileus, bowel obstruction
 - wound infection
 - MI/CVA
 - pneumonia
 - DVT/PE (most common cause of mortality)
- post-op (late)
 - ED
 - incontinence
 - lymphocele
 - inguinal hernia

What are the RFs for BN contractures?

- excessive blood loss
- urine leak
- prior RADs
- prior TURP
- tension on anastomosis
- poor mucosal apposition

What are the RFs for post-RP urinary incontinence?

- patient factors } **patient age**
 - } **pre-op voiding function**
 - } abN detrusor contractility
 - } prior TURP (controversial)
- disease factors } **pre-op or post-op RADs**
 - } **surgical technique (NS vs non-NS)**
 - } higher stage
 - } excessive blood loss
- other factors } surgeon experience

List 5 technical aspects to repairing a rectal laceration during RadP?

- 1) copiously irrigate wound with ABx solution
- 2) freshen edges & close in 2 layers with absorbable sutures (Gen Sx closes rectum in 1 layer only)
- 3) interpose omental flap
- 4) dilate anus (never done by Gen Sx)
- 5) drain

What are the indications for diverting colostomy after rectal injury during RadP?

- **diverting end +/- mucous fistula**
- 1) previous RADs
- 2) large defect ($\geq 1.5\text{cm}$)
- 3) gross fecal spillage
- 4) hx of long-term steroids

SURGICAL MODIFICATIONS TO CLASSIC ANATOMIC RADICAL PROSTATECTOMY

What modifications have been made to the classic RadP?

- 1) BN sparing technique } may have slightly earlier return of urinary control
 - } may have slightly higher BN contracture and BN +ve margin rates
- 2) SV sparing } may have better urinary continence & erectile function
 - } may have higher biochemical recurrence rates
- 3) nerve graft interposition } sural nerve, genitofemoral nerve
 - avg length of nerve needed per side is 5-6cm
 - nerve graft is reversed when sutured in with 7-0 prolene
 - } may have better urinary continence & erectile function
- 4) high anterior NVB release before division of DVC } nerves innervating EUS & cavernosal bodies may travel more anteriorly at apex than thought

SALVAGE RADICAL PROSTATECTOMY

What are the main options for local recurrence after RADs?

- 1) WW
- 2) cryosurgery
- 3) hormones
- 4) salvage Rad P

What are the eligibility criteria for salvage Rad P?

- patient with excellent health and life expectancy $>15\text{yrs}$
- no evidence of mets
- at initial presentation (before RADs) had unequivocally clinically localized PCa
- TRUS Bx, Gleason grade, DRE, serum PSA levels, etc all suggest localized disease

What are the predictors of progression after salvage RP?

- Bianco et al, Int J Rad Oncol Biol Phys '05
 - 1) pre-op PSA >10
 - 2) SV invasion
 - 3) +LN mets

What are the complications of salvage RadP?

- significantly improved in modern era
- rectal injuries only slightly more common (~5%) } if good bowel prep & small injury, primary repair may be possible
- urinary incontinence rates are still high } ~50% are incontinent (even higher after brachy)
 - } ~**20% need AUS (cf 1-2% post Rad-P)**
 - } ~30% develop an anastomotic stricture
- almost all get ED
- +ve margin rates higher
- hemorrhage more common
- fistula rate higher
- wound infections more common

Where are the most common sites for rectal injury during salvage RadP?

- apex
- wide dissection of NVB
- dissection of Denonvilliers' fascia near base of prostate

Chapter #98 – Radical Perineal Prostatectomy

SELECTION OF PATIENTS

Why has there been a renewed interest in Radical Perineal Prostatectomy (RPP)?

- 1) Partin tables allow for accurate prediction of disease stage and LN involvement
 - more selective use of staging lymphadenectomy
 - eg 10% risk of LN mets if
 - 1) T1c disease with PSA >10 + Gleason ≥ 7 (4+3)
 - 2) T2 disease with PSA >10 + Gleason 7 (3+4)
 - 3) T2 disease with any PSA + Gleason ≥ 7 (4+3)
- 2) advancement of laparoscopic surgery has allowed for Lap pelvic lymphadenectomy + RPP
- 3) anatomic techniques applied to RPP have resulted in improved post-op erectile function
- 4) better urinary continence
 - excellent visualization of urethral dissection and anastomosis
- 5) low morbidity, rapid convalescence, shorter OR times, shorter hospital stays

What are the indications to RPP?

- same as RRP } high likelihood of organ-confined disease + life expectancy >10yrs
 - nerve-sparing for most
 - non-nerve sparing based on intra-op findings
- if pelvic lymphadenectomy indicated, can be done laparoscopically prior to RPP

What are the contraindications to RPP?

- 1) severe ankylosis of hips or spine \ will need exaggerated
- 2) unstable artificial hip replacement / lithotomy position

What scenarios might make RPP more appealing than the standard retropubic RadP?

- 1) renal Tx
- 2) severe inflammation from mesh used for hernia repair
- 3) morbidly obese

PRE-OP CARE

What is the standard pre-op care for a RPP?

- full bowel prep } mechanical + ABx (neomycin po)
- group and screen } less blood loss so crossmatch not usually needed
- TEDs
- prophylactic Abx iv

POSITION



EXPOSURE OF THE PROSTATE & NERVE-SPARING DISSECTION & VESICourethRAL ANASTOMOSIS & CLOSURE

What are the main points of the RPP?

- exaggerated lithotomy position } curved Lowsley retractor placed transurethrally
- curvilinear incision made from just medial to R ischial tuberosity to just medial to L
 - don't extend beyond 3-o'clock and 9-o'clock position of anus
- blunt dissection used to develop ischiorectal fossa bilaterally and central tendon divided
- fibers of external anal sphincter dissected and retracted anteriorly
 - fibers not incised – Belt technique
- longitudinal muscle fibers of rectum identified
- plane leading to rectourethralis developed w/ gentle dorsal traction on rectum (damp sponge)
 - rectourethralis appears as strap of muscle tenting rectum ventrally (to perineal body)
 - external anal sphincter retracted anteriorly
- rectourethralis divided close to apex of prostate to allow rectum to fall dorsally
 - **watch for rectal injuries at this point**
- gentle anterior pressure on Lowsley retractor brings prostate into field of view
 - allows for blunt dissection of prostate from rectum in cephalad direction (between anterior and posterior leafs of Denonvilliers' fascia) → **risk of rectal injury**
- nerve-sparing } anterior layer of Denonvilliers' fascia incised vertically in midline from BN to apex; gentle lateral traction used to facilitate lateral dissection of NVB
- apex and urethra identified and NVB dissected away from urethra as they course distally
- urethra incised and anterior prostate freed to level of BN by sharp and blunt dissection
 - **watch for DVC found ventrally**
- bladder entered anteriorly and prostate transected from BN
 - **lateral pedicles divided close to prostate to preserve NVB**
- SVs and vas divided bilaterally and specimen removed from field
- vesicourethral anastomosis started on anterior aspect +/- posterior BN reconstruction
- check for hemostasis or rectal injury and place Penrose
- reapproximate levator ani, central tendon, and Colles' fascia then close skin

When is rectal injury most common during RPP?

- division of rectourethralis
- dissection of prostate off rectum posteriorly

POST-OP CARE

What is the routine post-op care after RPP?

- CF to start and advance as tolerated
- AAT
- nil per rectum
- prophylactic ABx until catheter removed
- Penrose removed POD#1
- Foley x ~2wks post-op
- most patients are home on POD 1 or 2

PATHOLOGIC OUTCOMES

How is RPP for cancer control?

- no significant difference from retropubic RadP
- similar +ve margin rates } **prostate base is most common +ve margin**
→ ?also anteriorly
- similar time to biochemical failure

MORBIDITY

What are the advantages & disadvantages of RPP compared to RRP?

<u>ADVANTAGES</u>	<u>DISADVANTAGES</u>
<ul style="list-style-type: none">- less blood loss- shorter hospital stay- less anastomotic strictures (1-8% cf 20%)- urinary continence may be better- cancer control comparable to RRP- better exposure of apex- useful if hostile abdo/pelvis	<ul style="list-style-type: none">- lower extremity neuropraxia (2-25%) (mainly sensory & transient)- rectal injuries more common (1-11% cf 2%)- fecal urgency/incontinence (3-18% cf 8%)- pelvic lymphadenectomy requires separate incision- very difficult if >100cc- may have higher rates of ED

Chapter #99 – Laparoscopic and Robot-Assisted Laparoscopic Radical Prostatectomy and Pelvic Lymphadenectomy

LAPAROSCOPIC & ROBOTIC-ASSISTED LAPAROSCOPIC RADICAL PROSTATECTOMY

What are the indications for LRP and RALP?

- identical to open RadP
 - $\leq cT2$
 - no evidence of mets

What are contraindications to laparoscopy?

→ **ABSOLUTE } } } “Bad Reasons CHAMP”**

- Bowel obstruction
- Retroperitoneal abscess
- Coagulopathy (uncorrectable)
- Hemoperitoneum or hemoretroperitoneum (massive)
- Abdominal wall infection
- Malignant ascites (suspected)
- Peritonitis (generalized)

→ **RELATIVE**

- morbid obesity
- extensive prior abdo/pelvic surgery
- large prostate size ($>100g$)
- prior pelvic RADs
- neoadjuvant hormones
- prior prostate surgery (TURP)

What are the different gas insufflants used to create pneumoperitoneum?

- 1) CO₂ } **not combustible and very soluble in blood (rapid reabsorption)**
 - } may cause acidosis and be an issue in pts with severe chronic respiratory disease
- 2) Helium } **inert gas that is not combustible and not an issue for respiratory pts**
 - } not very soluble in blood
- 3) Nitric oxide } combustible
- 4) room air

What are the advantages of CO₂ in laparoscopy?

- cheap
- rapid reabsorption
- colourless
- non-flammable
- odourless
- non-toxic } no harm to OR staff

What are the different methods to gain access into the peritoneum?

- 1) Veress needle
 - 2) open Hasson-technique
 - 3) Blind trocar insertion (mainly gyne)
 - 4) hand-port access } usually better if made after pneumo developed (fascia on stretch)
 - 5) visual-trocar (eg Visi-port)
- **need to close ports $\geq 10mm$ } no need to close 5mm or self-dilating ports (except in kids)**

What are the main physiologic effects of a pneumoperitoneum?

- 1) Cardiovascular
 - ↓'d CVP if pt has low atrial pressures } ↑'d CVP if pt has high atrial pressures (hypervolemic), but ↓'d once ≥20mmHg
 - ↑'d MAP
 - ↑'d CO at ~10mmHg but CO ↓'s when ≥20mmHg (decreased venous return)
 - ↑'d SVR
 - tachycardia (hypercarbia stimulates sympathetics)
 - arrhythmias (ventricular extrasystoles from hypercarbia)
 - bradyarrhythmias from vagal stimulation during initiation of pneumo
 - **dramatic hypoTN can occur upon insufflation (vaso-vagal response of pneumo)**
 - Rx - desufflate and remove Trendelenburg
- 2) Respiratory
 - ↑'d peak airway pressures
 - ↓'d FRC
 - ↓'d vital capacity due to Trendelenburg and pneumo
 - ↑'d pCO₂
- 3) Renal
 - ↓'d GFR at pressure ≥10 mmHg
 - **oliguria from decreased renal vein blood flow & direct renal parenchymal compression at pressures >10mmHg**
 - use of lasix, mannitol, IVF can decrease oliguria
- 4) Bowel
 - ↓'d mesenteric blood flow } rarely results in mesenteric thrombosis
 - less post-op ileus
- 5) Acid-Base status
 - hypercarbia
 - respiratory acidosis
- 6) Hormonal
 - less hepatic stress response than open surgery
 - less catabolic cytokine and opioid release than open surgery
- 7) Immunologic
 - less immunosuppression than open surgery
 - less tumour cell growth after lap surgery

What are the advantages & disadvantages of LRP/RALP?

ADVANTAGES	DISADVANTAGES
- less blood loss and transfusions	- longer OR times
- shorter hospital stay (barely)	- urinary continence may be worse
- less post-op pain (barely)	- higher costs

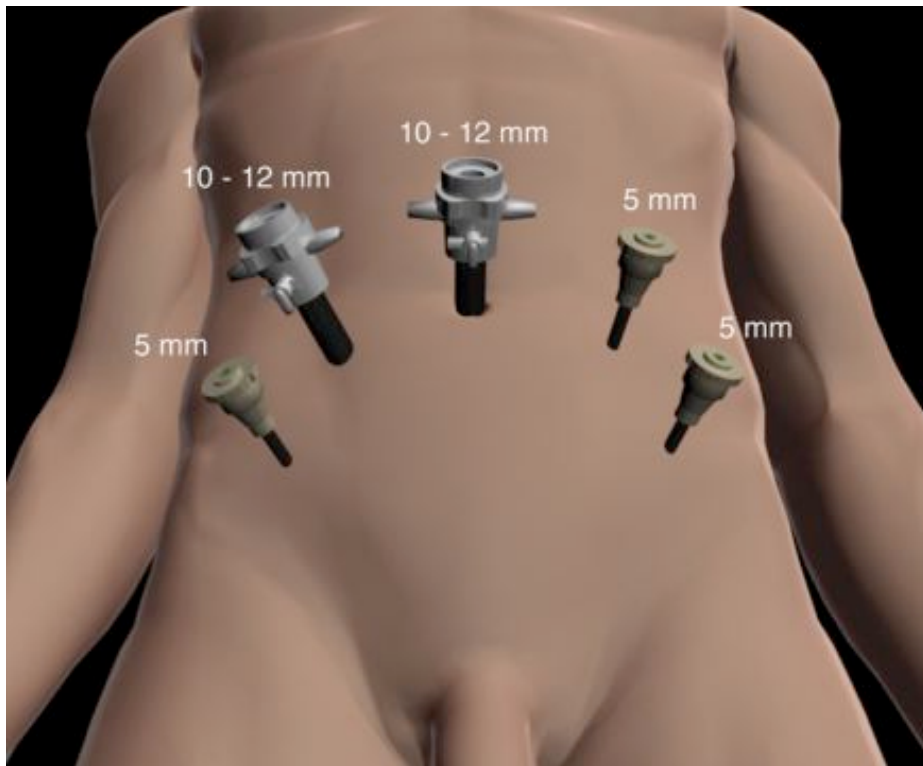
→ similar ED rates

→ similar oncologic outcomes } determined mainly by patient selection, surgeon experience

→ difficult to compare due to differences in pt selection, methods of collecting & reporting data, etc

What 3 factors have the greatest influence on cost of surgery?

- 1) OR time
- 2) length of hospital stay
- 3) use of disposables

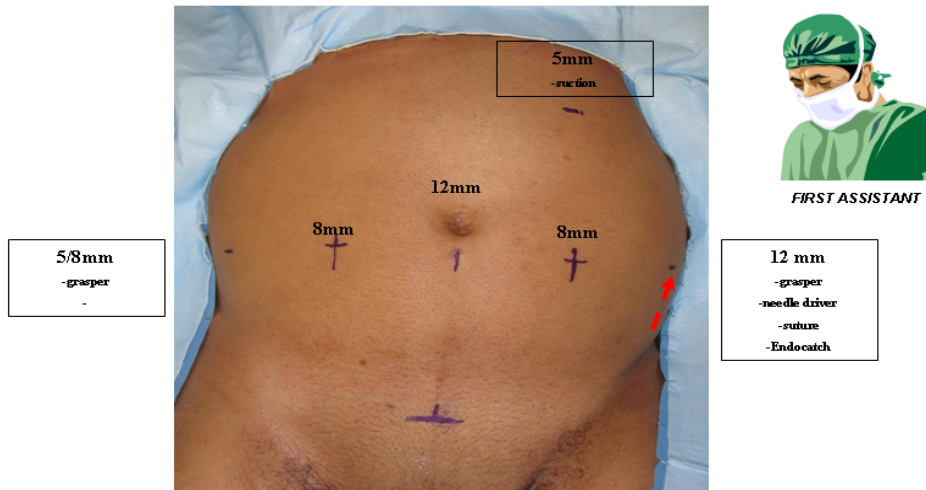


→ TROCAR CONFIGURATION FOR LRP



→ TROCAR CONFIGURATION FOR RALP } 12mm (camera), 8mm x3 (arms), 12mm RLQ (assistant)

Port Placement



All 10 steps of Robotic Radical Prostatectomy can be viewed online on
YouTube.com --> drkevinzorn

What are the main steps of the TRANSPERITONEAL LRP and RALP?

- dissection of SVs } either done first or done after prostate is dissected from BN
 - } first - Montsouris technique (LRP)
 - peritoneum overlying vas deferens incised sharply
 - vas transected & traced distally to SVs, which are dissected
 - } if done after BN transection - Menon technique (RALP)
 - separation of prostate from posterior BN followed by identification and dissection of SVs
- drop bladder off anterior abdo wall } divide urachus high above bladder & incise peritoneum bilaterally just medial to medial umbilical ligament
- develop space of Retzius and defat anterior prostate (bipolar)
- open endopelvic fascia and divide puboprostatics to expose levator muscle fibers
- sweep levators off surface of prostate and expose prostaticourethral junction
- DVC suture ligated w/ figure of eight 2-0 (can use metal sound to ensure urethra not sutured)
 - transected now or left for later
- back-bleeding stitch placed at anterior BN
- opening in levator fascia made sharply and NVB dissected free of prostate by developing interfascial plane (b/w levator and prostatic fascia)
- once NVBs are dropped away BN is incised (monopolar) to enter into bladder (use a sound as guide)
- SVs and vas may be divided now if not done earlier
- lifting SVs and vas, horizontal incision made b/w Denonvilliers' fascia and rectum
 - presence of perirectal fat confirms proper plane
- dissect plane between rectum and posterior prostate distally toward apex
 - careful dissection at this point will decrease risk of rectal injury later on after dividing urethra and freeing prostate from posteriorly attached rectum
- prostatic pedicles defined and taken using cautery +/- hem-o-lock clips OR temporary clamp occlusion followed by pedicle suturing
- once prostatic pedicle divided, dissection carried out to previously defined lateral NVB groove
- antegrade dissection of NVBs carried as distal as possible toward apex
 - can perform retrograde dissection of NVB } early transection of DVC + division of urethra at apex
 - } NVBs released from apex toward base
 - retrograde dissection may have greater risk of ongoing bleeding
- DVC transected carefully, being mindful of inadvertent entry into prostatic apex
 - may need additional DVC sutures
- NVBs dissected carefully off prostatic apex and urethra is cut and freed
- specimen placed in endocatch bag
- vesicourethral anastomosis made using either interrupted or running suture
- anterior or posterior tennis-racquet BN reconstruction performed if needed
- specimen bag removed via infra-umbilical port site
- close all ports $\geq 10\text{mm}$

What are the main steps of the EXTRAPERITONEAL LRP and RALP?

- pre-peritoneal plane entered via infra-umbilical incision
- 500-700cc balloon dilator used to develop space of Retzius
- rest of approach is similar except dissection of SVs and vas
→ SVs and Vas are always dissected after BN transection

How does the EXTRAPERITONEAL approach compare to the transperitoneal LRP/RALP?

→ most studies have found little to no difference in OR time and peri-op outcomes

→ ADVANTAGES

- shorter OR time
- shorter hospital stay
- earlier return of continence and less bladder dysfunction
- better if morbidly obese or if previous abdo surgery
- lower risk of bowel injury
- confines any urine leaks that may occur

→ DISADVANTAGES

- reduced working space
- potential for increased tension at the anastomosis (bladder fixed by urachus)
- higher CO₂ absorption

What are the potential complications of LRP/RALP?

→ overall complication rate 10-15% (cf <10% for open)

→ intra-op

- | | | |
|-------------------|--------------------------|--|
| - rectal injury | - ureteral injury | - bleeding |
| - vascular injury | - obturator nerve injury | - access related injury (bowel, vessels) |
| - urethral injury | - MI/PE/etc | - conversion to open (~1%) |

→ post-op (early)

- | | | |
|----------------------------|-------------------|-----------------------------|
| - urine leak (most common) | - wound infection | - DVT/PE (0.5% vs ~2% open) |
| - hemorrhage | - MI/CVA | - ileus, bowel obstruction |
| - UTI | - pneumonia | |

→ post-op (late)

- | | | |
|-------------------|-----------------------|----------------------------------|
| - ED | - lymphocele | - BN strictures (?less common 5% |
| - incontinence | - trocar site hernias | cf ~10% for open) |
| - inguinal hernia | | |

What factors are associated with a higher likelihood of conversion to open surgery?

- morbid obesity
- prior pelvic surgery
- prostatitis
- multiple TRUS Bx's
- prior TURP

Why are BN strictures and DVTs less common with LRP/RALP?

→ BN strictures } mobilization of bladder for tension-free anastomosis under direct vision

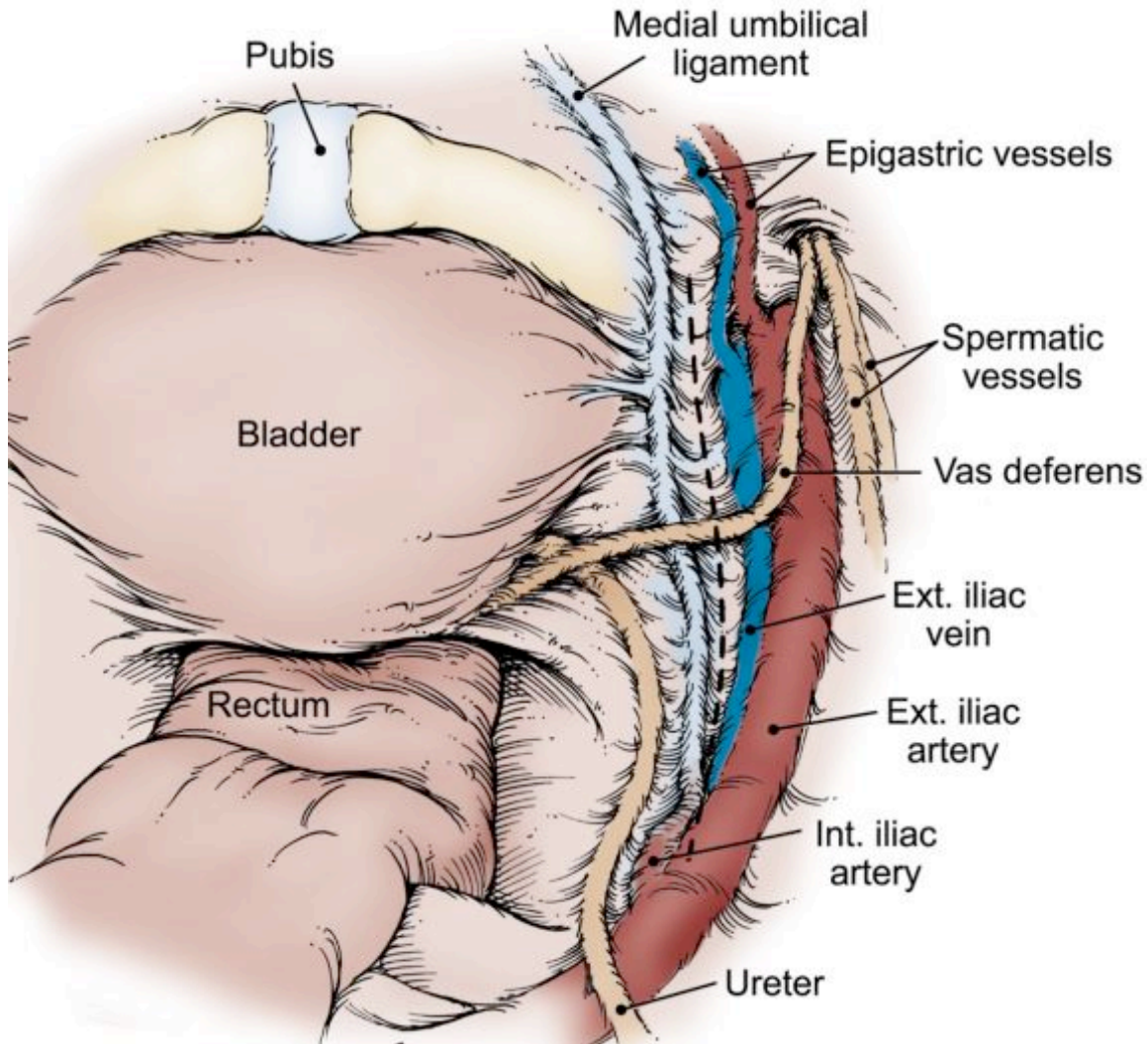
→ DVT } Trendelenberg positioning + lack of retractors compressing venous return

LAPAROSCOPIC PELVIC LYMPHADENECTOMY

What are the main steps of a laparoscopic pelvic lymphadenectomy?

→ can be done via transperitoneal or extraperitoneal route

- if done initially, incise peritoneum longitudinally just lateral to medial umbilical ligament from pubis to bifurcation of iliac vessels
 - avoid ureter at proximal end of dissection
 - vas must be clipped
- if done after prostatectomy, incision was already made medial to medial umbilical ligament when taking down bladder
- nodal packet grasped and retracted medially off external iliac vein
- dissection carried proximally to bifurcation of common iliacs and distally to node of Cloquet
- nodal packet retracted anteriorly and dissected off obturator nerve and vessels



→ LANDMARKS FOR LAPAROSCOPIC PELVIC LYMPHADENECTOMY

What are the potential complications after laparoscopic pelvic lymphadenectomy?

- overall, less common
- vascular injury (most common)
- obturator nerve injury
- ureteric injury
- lymphoceles } much less common, especially after transperitoneal approach
- DVT

Chapter #100 – Radiation for Prostate Cancer

LOCALIZED DISEASE

List the 3 risk groups for patients with clinically localized disease managed with EBRT.

→ based on AJCC 1992 staging

1) low risk

- stage <T2b
- PSA ≤10 ng/mL
- Gleason ≤6
- <33% +ve cores

\
/
/

>85% 5yr biochemical recurrence-free survival rates

2) intermediate risk

- stage cT2b
- PSA 10-20 ng/mL
- Gleason 7
- 33-50% +ve cores

\
/
/

~50% 5yr biochemical recurrence-free survival rates

3) high risk

- stage >T2b
- PSA >20 ng/mL
- Gleason ≥8
- >50% +ve cores

\
/
/

~33% 5yr biochemical recurrence-free survival rates

→ most in intermediate group can be classified into low or high risk group based on the % of +ve Bx cores in addition to PSA level, Gleason score, and clinical stage (AJCC '92)

→ if ≥50% +ve cores then RR of PCa-specific mortality after EBRT is 5-10 fold higher for low risk and favorable intermediate risk group

What pre-treatment factors predict recurrence (clinical & biochemical) post-EBRT?

- 1) PSA level
- 2) Gleason score
- 3) clinical stage (AJCC '92)
- 4) % of positive Bx cores } also found to predict time to biochemical failure

What post-treatment factors predict recurrence post-EBRT?

- PSA nadir value } **strongest independent RF for failure**
 - absolute threshold unknown but good if <0.5ng/mL
 - nadir >2ng/mL likely means distant failure
- time to PSA nadir } slower/longer time to nadir better
 - time to failure <12mos likely means distant failure
- post-nadir PSA DT } associated with type of failure
 - shorter/faster DT (<3-6mos) likely means distant failure

What is the ASTRO criteria for defining biochemical failure post-RADs?

- **3 consecutive increases in PSA, with each measurement of PSA 3-4 months apart in the first 2 yrs after RADs, and every 6 months after 2 yrs**
 - date of failure should be backdated to midway between PSA nadir and date of first increase
 - requirement for 3 readings and temporal spacing allows for temporary instability related to fluctuations due to benign etiology

What are some of the criticisms of the ASTRO criteria for defining biochemical failure post-RADs?

- waiting for 3 consecutive rises delays Dx of failure
 - argument } nobody needs treatment during this time anyways
- backdating of failures with status being “success” during the f/u underestimates late failures and may overestimate treatment success
 - long f/u minimizes this effect

What is the PHOENIX criteria for defining biochemical failure post-RADs?

- **≥2 ng/mL rise in PSA above the post-RADs nadir**

What is the significance of the nadir value post-EBRT?

- level of PSA nadir reflects likelihood of failure as well as type of failure
- the higher the nadir, the more likely is distant failure
- median PSA nadir in men that remain NED is approximately 0.4-0.5 ng/mL
- **median PSA nadir in men with local failure is often 1-2 ng/mL**
- **median PSA nadir in men with distant failure is often >2.0 ng/mL**

What is the significance of the time to nadir post-EBRT?

- lower nadir and longer time to nadir are independent predictors of freedom from distant mets
- the shorter the time to nadir, the more likely is distant failure
- median time to nadir in men that remain NED post-Rads is 22-34 months
- **median time to nadir in men with local failure is 12-18 months**
- **median time to nadir in men with distant failure is <12 months**

What is the significance of the post-nadir DT of the PSA post-EBRT?

- DT of PSA correlates with type of failure
- shorter PSA DT most likely represents distant failure
- **longer PSA DT associated with local failure } DT ~12 months**
- **shorter PSA DT associated with distant failure } DT ~3-6 months**

What are the 3 potential sources of PSA that contribute to the nadir post-EBRT?

- 1) residual benign prostatic epithelium
 - lower and longer time to nadir (eg nadir <0.5 ng/mL with time to nadir >2yrs)
- 2) residual local PCa cells
- 3) subclinical micromets
 - higher and earlier nadir (eg nadir >2ng/mL with DT <3 months)

What is the importance of neoadjuvant hormones and defining biochemical failure post-EBRT?

- neoadjuvant or concurrent ADT often results in an undetectable PSA prior to RADs
- with rapid recovery of serum testosterone, there may be a temporary increase in PSA shortly after completion of RADs and cessation of hormones
- using ASTRO definition usually allows for this phenomenon to pass and to avoid incorrectly labeling the patient as a RADs failure

What is the PSA bounce?

- **defined as a rise >0.2 ng/mL followed by a durable decline**
- **occurs most commonly after brachy } ~25-35%**
 - more common in younger men and with use of 125I (rather than 103Pd)
 - spike usually occurs from 9-30 months post-brachy and can last 12-18months
 - **most show cumulative rise of no more than 2-3 ng/mL } MILD**
- due to presence of residual benign prostate or before full effect of RADs or radiation prostatitis

What are the important issues regarding post-RADs prostate Bx?

- 1) timing of Bx with respect to completion of RADs
 - optimal time to biopsy is **30-36months post-RADs** (Crook et al, Urology '95)
- 2) interpreting indeterminate Bx results which show residual tumour with marked radiation effects and uncertain viability
 - should only give Gleason score with minimal or absent histologic evidence of radiation effect
 - benign glands with radiation induced atypia can mimic malignancy
 - Anti-cytokeratin monoclonal Ab for HMWK labels the basal cell layer of benign glands & can be used to r/o malignant cells (which have NO basal cell layer)
- 3) the usefulness of markers of cellular proliferation
 - proliferative cell nuclear antigen (**PCNA**)
 - unstable in formalin (unreliable)
 - **Ki-67**
 - reliable despite tissue being preserved in formalin
- 4) the uncertainty imposed by sampling error
 - false negative rates approach 20% because surviving malignant cells may be in the form of minimal scattered micro-foci

What is the grading scheme used to score degree of radiation effect?

- important to differentiate b/w Bx showing no or minimal RADs effect & those showing marked treatment effect
- should only give Gleason score with minimal or absent histologic evidence of radiation effect
- cytoplasmic (0-3) and nuclear (0-3) scores are added together
 - 5-6 = marked treatment effect
 - 3-4 = moderate
 - 0-2 = minimal

TREATMENT: CANCER CONTROL AND QUALITY OF LIFE

EBRT

What is the role of RADs in men with PCa?

- 1) primary therapy
- 2) post-RP adjuvant
- 3) post-RP salvage
- 4) palliation

What are the contraindications to EBRT for PCa?

- **ABSOLUTE** } previous pelvic RADs
- **RELATIVE** } previous TURP
 - } severe LUTS
 - } IBD

What is the RTOG scale for late GI and GU morbidity post-EBRT?

Grade	GU	GI
1	- symptoms not needing Rx	- symptoms not needing Rx
2	- moderate frequency - generalized telangectasia - intermittent gross hematuria	- >2 anti-diarrheals per wk - regular non-narcotics for pain - occasional blood transfusions - occasional steroids - occasional dilation and use of pads
3	- severe frequency and dysuria - severe generalized telangectasia - frequent hematuria - reduction in bladder capacity (<150 mL)	- >2 anti-diarrheals per day - regular narcotics for pain - frequent blood transfusions - steroid enemas - regular dilation and use of pads
4	- necrosis - contracted bladder (<100 mL) - severe hemorrhagic cystitis	- perforation - life-threatening bleeding - need for GI surgical repair
5	- fatal toxicity	- fatal toxicity

- grade 1 = no Rx
- grade 2 = mild + occasional Rx
- grade 3 = moderate + frequent Rx
- grade 4 = severe
- grade 5 = death

→ most late rectal complications are seen within 2yrs, almost always within 4yrs

→ late GU complications are harder to identify & follow because they manifest so many years later

What are the potential side effects of EBRT?

- 1) ED } worsens with time (40-55% ED at 5yrs)
 - 2) incontinence
 - 3) GI symptoms (diarrhea, rectal pain, rectal bleeding, tenesmus, etc) }
 - 4) LUTS (frequency, dysuria, etc) }
 - 5) gross hematuria from radiation cystitis }
 - 6) urethral stricture }
 - 7) prostatic-rectal fistula }
 - 8) radiation-induced skin dermatitis }
 - 9) secondary malignancies }
- GI toxicity worse w/ EBRT than w/ brachy**

How common are complications following EBRT?

→ **depends on type of EBRT and also dosage**

- 3D conformal } 5-20% with moderate to severe GI complications
- } 5-20% with moderate to severe GU complications

List the causes of hemorrhagic cystitis.

→ “CRIS PACE(NB) BACKS CAR”

→ CHEMICAL

- **Penicillins**
- **Allopurinol**
- **Cyclophosphamide & Ifosfamide (acrolein)** } usually occurs within 48hrs
- **Ether**
- **NSAIDs**
- **Bleomycin**

→ **RADIATION**

- can present months to yrs later
- no good treatment } hyperbaric O2, hyaluronic acid, steroids, estrogens

→ INFECTIOUS

- **BK virus** (most common virus associated with hemorrhagic cystitis)
- **Adenovirus** (types 11 & 35)
- **Candidal** cystitis
- **KEEPS bacterium** (Klebsiella, Enterobacter, E. coli, Proteus, Staph saprophyticus, etc)
- **Schistosomiasis haematobium**

→ **SYSTEMIC DISEASES**

- **Crohn's disease**
- **Amyloidosis**
- **Rheumatoid arthritis**

What are the treatment options for hemorrhagic cystitis?

➔ Please BE A SAFE DOC"

- **PGs** (for cyclophosphamide)
- **Burn** with cautery
- **Elmiron**
- **Alum 1%**
- **Silver nitrate**
- **Amicar** (iv or instillation) } ?not available
- **Formalin**
- **Embolization**
- **Diversion +/- cystectomy**
- **O2** (hyperbaric)
- **Cold CBI**

What was the main benefit of 3D conformal EBRT over conventional EBRT?

→ randomized studies comparing the two } Koper et al '99 (Rotterdam)

} Dearnaley et al '99 (Royal Marsden)

- **significant reduction in minor GI side effects** } especially rectal toxicity
- no significant difference in minor GU side effects
- trend toward improved sexual function
- **improved PSA-free survival**

How successful is 3D conformal EBRT for PCa?

- long term data not yet available
- U of Michigan '97
 - 707 pts with 3D conformal EBRT (up to 80Gy, most >69Gy)
 - 75% 5yr biochemical relapse free survival for favorable PCa (T1-2, ≤G6, PSA <10)
 - 35% 5yr biochemical relapse free survival for unfavorable PCa (T3-4, ≥G7, PSA >10)

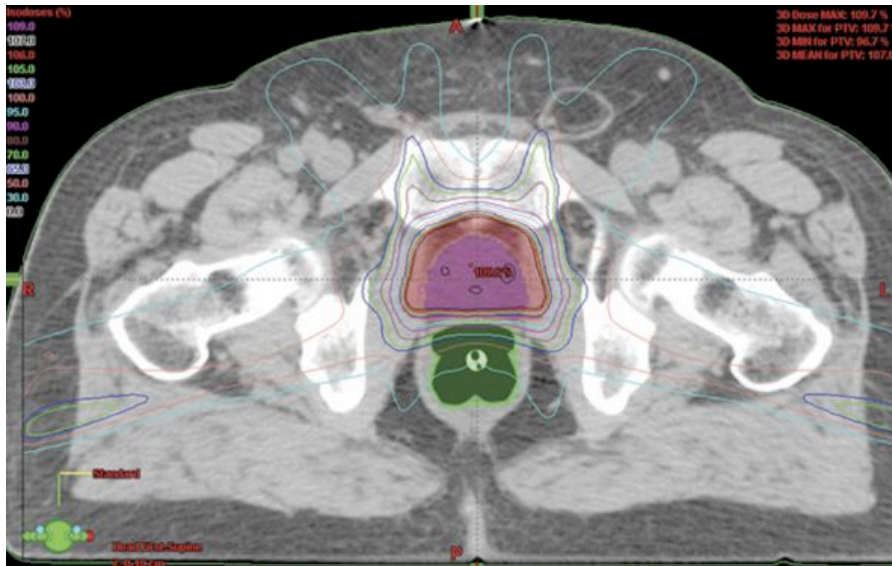
What is the role of dose-escalation in EBRT?

→ standard 3D conformal EBRT was ~70Gy } dose can be escalated to >75Gy

- no benefit in low risk patients (Gleason 6, stage T1 or T2a, PSA <10 ng/mL)
→ all patients do well in this group
- no benefit in high-risk group (Gleason ≥7, stage T2b or T3, PSA >20 ng/mL)
- all other groups showed statistically significant improvements in PSA relapse-free rates
→ greatest benefit in patients with pre-treatment PSA >10 ng/mL

What is IMRT?

- intensity-modulated radiation therapy
- use of inverse treatment planning via simulated annealing (mathematical optimization technique) to achieve a precise, non-uniform beam confluence
 - allows maximized treatment to the target while minimizing treatment to surrounding tissues
- also uses computer-controlled intensity modulation of the radiation beam during treatment
 - results in a set of radiation beams with changing intensities across the field
- IMRT allows delivery of statistically significantly lower doses to critical normal tissue



→ Intensity-modulated radiotherapy (IMRT)

What are the benefits of IMRT over conformal EBRT?

- allows **delivery of escalated doses of radiation with a reduction in GI & GU toxicity**
 - statistically significant difference in both rectal and bladder toxicity
- allows decreased RADs to penile bulb, theoretically improving ED rates post-IMRT
- better cancer control outcomes
 - can deliver higher doses with less toxicity

What are the potential advantages & disadvantages with the use of HEAVY PARTICAL BEAMS?

→ **current standard is electron beam RADs, created by linear accelerators**

→ other heavy particles such as protons, neutrons, helium ions, heavy ions (neon, argon, carbon) and negative ions are also available

→ advantages

- more densely destructive & exhibits **Bragg peak** (sharp cutoff in dose at end of particle range)
 - ??? less collateral damage at higher doses of radiation
- damage they create is less easily repaired by tumour cells

→ disadvantages

- difficult to produce and to control beam
- limited gain in tumour control
- cost

Brachytherapy

What are the ASTRO criteria for eligibility for brachytherapy?

- PSA <10
- Gleason ≤ 6
- clinical stage $\leq T2a$
- gland size <50g
- IPSS <7
- Qmax >10 cc/sec

What are the contraindications to brachytherapy?

- high-volume, high risk PCa } doesn't meet ASTRO criteria for low risk disease
 } unless part of study (with EBRT boost)
- large prostate (>50g) } pubic arch may interfere with seed placement
 } sometimes hormones used to shrink prostate (can affect outcomes)
- very small prostate (<20g) } hard to implant seeds
- severe LUTS (IPSS >7 or Qmax <10cc/sec)
- large median lobes
- previous TURP } higher risk of superficial urethral necrosis & seeds don't stay

Why does brachytherapy have a very rapid dose falloff (few millimeters)?

- [illegible]

Who pioneered the current method of brachytherapy?

- Whitmore et al was the first to implant ¹²⁵I seeds into the prostate in the '70s
→ retropubic approach to prostate after pelvic LN dissection } “freehand” implantation
- Holm et al first described the closed transperineal implantation with the aid of TRUS in '83
→ use of template & stabilizer } radioactive seeds deployed as needle is withdrawn
- dosimetric plans are based on pre-op TRUS (Blasko '93), intra-op TRUS (Kaplan '00),
pre-op CT (Koutrouvelis '98), or intra-op MRI (D'Amico et al '98)
→ intra-op real-time dosimetry is best

What are the different radio-isotopes used for brachytherapy?

- no significant difference in outcomes between isotopes
- **¹²⁵Iodine** } most commonly used isotope
 - (145 Gy) } emits low-energy x-rays (27 keV)
 - } **T_{1/2} is 59.6 days → need to wait 9 months if need TURP, cystectomy, etc**
- **¹⁰³Palladium** } emits low-energy x-rays (21 keV)
 - (125 Gy) } T_{1/2} is 17 days → shorter half-life so need higher activity seeds
 - } **used more often for high grade PCa (≥Gleason 8) & patients getting an implant boost post-EBRT**

How successful is brachytherapy monotherapy?

- [illegible]

What is the role of brachytherapy + EBRT?

- usually used for patients with higher stage disease
 - no benefit over brachytherapy monotherapy for low-risk disease
- brachytherapy used as a boost either pre- or post-EBRT
- brachy seed dose is usually lower } generally 60-70% of monotherapy dose
- EBRT dose is also lower } 41 to 45 Gy delivered
- 5yr biochemical-recurrence free survival 90-95%
- 10yr biochemical-recurrence free survival 70-75%

What is high-dose-rate (HDR) brachytherapy?

→ uses high-activity ^{192}Ir sources that emit gamma radiation at 400 keV

- needles implanted transperineally under TRUS-guidance
- CT used to locate needle position and to calculate dosimetric plan
- under computer guidance, ^{192}Ir sources are placed into needles for seconds to minutes
- precise dose administered by varying dwell times (patients admitted in special rooms, etc)
- used primarily in combination with EBRT for intermediate- and high-risk PCa
- delivered as a boost in 2-4 sessions, either pre- or post-EBRT

How successful is HDR brachytherapy + EBRT?

- no significant benefit in low-risk PCa over permanent seen implants
- still under investigation for intermediate- and high-risk disease

How is implant quality assessed post-brachytherapy?

→ can use post-implantation imaging using CT or MRI

- D90 } minimal dose covering 90% of the prostate volume
 - V100 and V150 } % volume of prostate receiving 100% and 150% of prescribed dose
- timing of post-implantation imaging is not important } prostatic edema is minimal

What is the significance of a +ve post-brachy prostate Bx?

→ occurs in 3-20%

- if obtained within first 2yrs after brachy, result can be questioned

Which pts are at increased risk of complications post-brachy?

- prior EBRT
- prior TURP
- seeds closer than 7mm to rectum
- seeds close to urethra
- severe LUTS (high IPSS)
- history of prostatitis
- prostate size > 60g

What are the complications of brachytherapy?

→ Acute

- urinary retention: 1-5% } 96% void spontaneously after Foley removed
 } 5% require alpha blockers for > 1month
- LUTS } **higher rate of GU toxicity compared to external beam RT**
 } IPSS increases significantly after brachy, remains high x 3months
 } worse LUTS w/ larger prostates (> 60cc)
 } risk of LUTS is a function of the urethral length receiving high dose
- proctitis } usually self-limiting

→ Chronic

- rectal toxicity } rectal bleeding due to radiation proctitis
 - } minor bleeding in 1-4%, significant complication in <1%
 - } colostomy rate of 0.3%
 - gracilis muscle interposition flap to repair prostatico-rectal fistula (York-Mason is 2nd choice)
- ED } potency rates better than EBRT (significant drop-off seen after 3-4 yrs)
 - } potency maintained in 79% of brachy pts vs. 68% EBRT (Zelevsky 1999)
 - } Viagra works in 80% of pts w/ ED post-brachy
- UI
- LUTS
- seed migration
- hematuria
- urethral stricture

What are the potential side effects of brachytherapy?

→ based on implant technique (excluding TZ, intentionally placing seeds outside capsule, etc)

1) GU toxicity

→ assessed using IPSS

- brachy usually safe after TURP
- most report grade I urinary toxicity in first 1-2 months
- significant obstruction needing CIC occurs in <5%
- overall need for surgical management occurs in 2-3%
 - post-brachy TURP can be done with low rate of post-TURP incontinence
- larger glands (>60g) and those w/ high pre-op IPSS (>20/35) have higher chance of urinary toxicity and AUR
- use of α -blockers pre-op may decrease severity and duration of urinary symptoms

2) GI toxicity

→ assessed using RTOG toxicity grading scale

- usually self-limiting
- rate of minor proctitis and rectal bleeding is 1-4%
- rate of significant rectal complications is <1%

3) sexual dysfunction

→ assessed using IIEF

- better early rates of potency than EBRT and RP
- a continued drop-off in potency seen with continued follow-up past 3yrs
- ~50% ED rate at 6yrs post-brachy in men that were fully potent pre-op

Locally advanced disease

What is the role of neoadjuvant ADT + RADs for locally advanced PCa?

→ **neoadjuvant ADT may reduce target volume and may potentially act as radio-sensitizer**

→ appears to be appropriate in very high-risk patients

→ Pilepich et al, Int J Radiat Oncol Biol Phys '01

- 471 men with cT2-4 tumours
- randomized to RADs alone OR Zoladex + flutamide for 2mos before & during RADs
- 4mos ADT associated with reduction in distant mets and improved local control
- 4mos ADT had better PCa-specific survival and PSA-free survival
- no difference in overall survival, although some survival benefit seen in men with Gleason 6

What is the role of adjuvant ADT and RADs for locally advanced PCa?

→ **benefits those with very high risk disease**

→ short period of ADT good for intermediate-risk PCa but more prolonged ADT better for high-risk PCa

→ **6mos for localized intermediate-risk & 3yrs for localized high-risk or locally advanced**

→ Bolla et al, NEJM '97 with update in Lancet '02

- RCT of 401 men with locally advanced PCa (80% had T3 disease)
- only study to show overall survival benefit
- 3yrs of adjuvant goserelin (Zoladex)
- 5yr overall survival 78% in adjuvant ADT group vs 62% in RADs-only group

What is the ideal dose and extent of RADs for locally advanced PCa?

- doses >72Gy likely more effective
- some studies to show whole-pelvis RADs better for progression-free survival but not overall survival
- HDR brachy + EBRT less well studied but may have a role

What is the role of chemo and RADs for locally advanced PCa?

- less well studied than RP and chemo } promising improvements that require more study

Node positive disease

What is the role for EBRT in node +ve PCa?

- a few studies have shown benefit with combination RADs + ADT
- may be beneficial for men with grossly +ve LNs on staging imaging
 - Sands et al (1995), Whittington et al (1997), Buskirk et al (2001), Zagars et al (2001)
- may also be beneficial in men found to have lymphadenectomy-proven +ve LN mets
- improved biochemical relapse rate, cause-specific mortality rate, and overall survival rate
- benefit likely seen in patients with micromets

Bone Mets

How successful is palliative RADs for bone pain?

- **overall response rates of 85-100%**
- single-fraction regimen (8Gy) appears as effective as other longer regimes but is also associated with increased acute morbidity (particularly abdominal organs)
 - **often given 30Gy in 10 divided doses to decrease S/Es**

What are the indications for prophylactic surgical fixation of a bone met?

- **all need post-op RADs**
- 1) intramedullary lytic lesion $\geq 50\%$ of the cross-sectional diameter of the bone
- 2) lytic lesion involving a length of cortex \geq cross-sectional diameter of the bone or $> 2.5\text{cm}$ in axial length
- 3) pathologic fracture of weight-bearing bone

What is the management of pathologic fractures?

- **not common because PCa produces primarily blastic mets**
- surgical fixation required for pain control and to promote healing
- all cases need post-op RADs

How does metastatic spinal cord compression present?

- **pain (95%)**
- leg weakness, numbness, pain (if paralysis present on admission, likely permanent)
- bowel and bladder dysfunction
- autonomic dysfunction

What is the management of metastatic spinal cord compression?

- medical emergency
- investigations
 - Hx and P/E
 - imaging (MRI)
- management
 - steroids (dexamethasone) } 10mg iv loading dose followed by 4-24mg iv/po q6h
 - } improves pain and decreases vasogenic edema
 - ketoconazole } 400mg q8h (watch for adrenal crisis)
 - } fastest non-surgical way to get castrate level of T → consider B/L orchiectomy
 - RADs
 - surgery + RADs } may have better outcomes in subset
 - systemic radionuclides

What are the indications for spine Sx on HRPc patients with cord compression?

- | | |
|---|-------------------------------------|
| 1) evidence of progression during RADs (signs & symptoms) | 5) extensive bone involvement |
| 2) recurrence after RADs | 6) compression caused by bone |
| 3) unstable pathologic fractures | 7) unknown tissue diagnosis |
| 4) high-grade epidural blocks | 8) hx of previous RADs to same area |

What are the different systemic radionuclides used for bone mets?

- ³²P Phosphorus } 60-80% response rate w/ ~5month duration but ++ toxicity
- ⁸⁹Sr Strontium } 60-90% response rate w/ ~6month duration (longest half-life at 50days)
- ¹⁸⁶Re Rhenium } 75-80% response rate w/ only 1-2month duration
- ¹⁵³Sm Samarium } 75-90% response rate w/ only 2-3month duration (shortest half-life at 46hrs)

Table 100-9 -- Physical Characteristics of Radionuclides Reviewed

Radiounclide	Physical Half-Life	Beta Energy (MeV)	Gamma Energy (keV)	Chelate
³² P	14.3 days	1.71	0	Orthophosphate
⁸⁹ Sr	50.6 days	1.46	0	Chloride
¹⁸⁶ Re	90.6 hours	1.07	137	HEDP
¹⁵³ Sm	46.3 hours	0.84	103	EDTMP

How successful is ⁸⁹Sr in the treatment of bone mets?

- 60-90% response rate } moderate or good relief of pain
- ~6month duration
- S/Es } thrombocytopenia

What are the conditions of metastatic PCa that can be treated with palliative RADs?

- bone mets
- brain mets
- spinal cord compression
- pathologic fractures

Gene Therapy for PCa

What is the potential role of gene therapy and Rads for PCa?

- may enhance or complement radiation-induced cell killing
- may have a role in locally recurrent PCa post-radiation therapy

What are the 3 main categories of genetic therapies applied to PCa?

- 1) corrective therapy
 - functional complementation of abN or absent genes into a cell
- 2) immunotherapy
 - improving tumour antigen presentation to the host immune system
- 3) cytolytic or pro-apoptotic therapy
 - a) enzyme/prodrugs ("suicide gene" therapy)
 - b) oncolytics
 - c) cytotoxins

What are the advantages of cryoablation of PCa?

- focal application with sparing of many normal tissues
- treatment of unresectable cancers (even T3)
- minimal bleeding
- local anesthetic effect
- predictable freezing pattern
- can be repeated

TECHNICAL IMPROVEMENTS IN CRYOTHERAPY EQUIPMENT

What are some of the important technical improvements in cryotherapy?

- 1) biplanar TRUS } can see leading edge of frozen tissue in transverse and longitudinal views
- 2) template and stands
- 3) transition to pressurized gas } liquid nitrogen is coldest cryo agent but can't be used in probes <3mm
 } use of gas permits ultra-thin probes
 → argon for cooling & helium for heating
- 4) thermocouples } can measure temp at edges of treatment zone
- 5) urethral warming device } protects urethra and EUS
 → decreases urethral sloughing & prevents incontinence
- 6) computerized planning systems

PATIENT SELECTION

What are the contraindications for primary cryotherapy for PCa?

→ ABSOLUTE

- 1) extensive periurethral disease (won't be treated well due to urethral warmer)
- 2) fistulae (eg IBD)
- 3) hx of pelvic surgery or trauma (distorts prostate anatomy)

→ RELATIVE

- 4) gland >50g (complete freezing difficult & may need neoadjuvant hormones)
- 5) prior TURP with large defect
- 6) high IPSS
- 7) major rectal pathology (eg rectal stenosis, APR, etc)

Which patients are eligible for primary cryotherapy for PCa?

→ mainly an alternative to EBRT

- 1) any Gleason grade
- 2) +ED or not interested in erectile function
- 3) up to T3 disease (should be small volume disease)
- 4) pt ineligible or refusing RP or EBRT or brachy

What are the salvage options for recurrent PCa post-RADs?

- salvage RP
- cryotherapy
- brachy
- hormones

What are the indications for salvage cryotherapy for PCa?

- rising PSA
- Bx proven recurrence
- no evidence of mets

→ in salvage setting, there is a poor response if PSA >10ng/mL (similar to salvage Rad P)

SURGICAL TECHNIQUE

Describe the basic steps of prostate cryotherapy

- pre-op } light bowel prep + enema morning of
 - } neoadjuvant hormones if gross ECE, SV invasion, or prostate >50g
 - } consider regional LN dissection if high risk for LN mets
- intra-op } exaggerated dorsal lithotomy
 - } clamped Foley initially
 - } biplanar TRUS + computerized planning system
 - } direct transperineal placement of cryoprobes using template and TRUS-guidance
 - } +/- thermocouples
 - midgland, EUS, NVB, Denonvilliers' fascia
 - maintain temp >15C at EUS
 - } cystoscopy to assess urethra
 - make sure no probes in urethra
 - } +/- S/P tube insertion
 - } urethral warmer inserted over guidewire
 - } freezing started at the anterior probe layer and continued posteriorly
 - starting anterior maintains TRUS visibility
 - **2 freeze-thaw cycles necessary**
 - } urethral warmer exchanged for Foley
- post-op } home on Abx, pain meds, and α -blocker x1 month
 - } Foley out in 2-3 days
 - } if S/P placed, clamped after 3 days
 - removed once normal voiding regained

PATIENT FOLLOW-UP

What happens to serum PSA post-cryotherapy?

- initially goes up (release of intracellular PSA from cellular necrosis)
- should nadir by 3 months
- biochemical failure post-cryo is not defined } 0.3, 0.4, 0.5, 1.0, or ASTRO criteria (3 rises)

What is the TRUS appearance of the prostate after cryo?

- no difference immediately
- at 3 months } necrosis, heterogeneous echo pattern
- at 6 months } small gland with obscured boundary consistent with periprostatic fibrosis

OUTCOMES AFTER PRIMARY CRYOTHERAPY

How common is a +ve prostate Bx post-cryotherapy?

- **overall 7-25% } recurrence more common at SVs and apex**
- dependant on initial stage } much higher with T3 disease
- also depends on # of freeze-thaw cycles } more common if only 1 cycle (30-60%)
- also related to PSA nadir
 - 50% +ve Bx if PSA nadir was >0.5 ng/mL
- use of thermocouples also significantly reduces rate (~80% if no thermocouples used)

How common is biochemical failure?

- lowest in patients that achieved lower nadirs
→ only 20% recurrence if PSA nadirs <0.1 ng/mL
- 60-90% biochemical disease-free rate at 5yrs

How does cryotherapy compare to EBRT and brachy?

- similar biochemical disease-free rates
- similar +ve Bx rates
- **significantly higher rates of ED } 90% with cryotherapy**
- fistula rate similar to EBRT, but higher than brachy
- similar incontinence rates
- similar to EBRT for intermediate and high-risk PCa

What are the advantages of cryotherapy over some of the other local therapies?

- can destroy cancer cells that are radio-resistant & hormone-resistant
- can treat more extensive & aggressive tumours than brachy
→ can extend beyond capsule
- can be repeated with minimal morbidity

OUTCOMES AFTER SALVAGE CRYOTHERAPY

What are the prognostic factors that predict failure of salvage cryotherapy post-RADs?

- 50-70% biochemical recurrence-free rate at 12-18months
- PSA >10 ng/mL
- recurrent PCa with Gleason sum ≥9
- hormone-refractory local recurrence
- higher pre-RADs clinical stage

How does salvage cryotherapy compare to other forms of salvage therapy?

- not as effective as salvage RP but has minimal morbidity
- similar results to salvage brachytherapy

What are the predictors of progression after salvage Rad P?

- Bianco et al, Int J Rad Oncol Biol Phys '05
 - 1) pre-op PSA >10
 - 2) SV invasion
 - 3) +LN mets

MANAGEMENT OF LOCAL RECURRENCE AFTER CRYOTHERAPY

What are the options following failed primary cryotherapy?

- repeat cryotherapy
- salvage RADs
- salvage RP

ADJUNCTIVE THERAPY

What potential adjuvant therapies are available with cryotherapy?

- no therapy has proven beneficial in adjuvant setting post-cryotherapy
- 1) RADs } cooled cells may have greater sensitivity to radiation
- 2) CHEMO
- 3) intra-prostatic cytotoxic injections } investigational

COMPLICATIONS

What are the potential complications of prostate cryotherapy?

- 1) **ED** } **>80%**
- 2) incontinence } ~5%
 - } higher rates with prior TURP
 - } ~10% after salvage cryotherapy (much lower than salvage RP)
- 3) urethral sloughing } <5%
- 4) urethral strictures } rare if urethral warmer used
- 5) pelvic or rectal pain } <10%
 - likely from osteitis pubis from frozen pubis
 - must r/o urinoma or abscess
- 6) penile numbness } usually transient
 - from dorsal nerve neuropraxia
- 7) rectourethral fistula } <1%
 - **most common in those with previous hx of RADs**
 - watery diarrhea, pneumaturia, or fecaluria
- 8) ureteric injury } rare to see hydronephrosis
 - if cryoprobe is placed near BN or deep into SVs
- 9) SBO } <1%
 - occurs only if iceball extends into peritoneum (cul-de-sac)

QUALITY OF LIFE AFTER CRYOTHERAPY

What is the QOL after cryotherapy for PCa?

- QOL scores at 1yr are similar to RadP, RADs, observation
 - significantly worse early on with steady increase over the yr
 - sexual function scores significantly worse than baseline at 1yr
- significantly worse after salvage cryotherapy

NATURAL HISTORY

What is the natural history of locally advanced PCa?

- overall survival is 10-92% at 5yrs and 14-78% at 10yrs } significant variability
- VACURG } 58% overall survival at 5yrs
- MRC study } median time to progression was 10 months
 } median time to death 4yrs
- Johansson et al, JAMA '97 } 15yr survival was 57% for men with locally advanced PCa
- if left unRx'd, men with high-risk PCa are at significant risk of disease progression & PCa-specific death

What are the predictors of PCa progression?

→ post-RP

- 1) pre-op } clinical stage
 } Gleason score
 } pre-op PSA
- 2) pathologic } pathologic stage (most important)
 → T3a, T3b, +LNs
 } Gleason score
 } margin status (very important)
 } LVI and PNI

→ post-RADs

- 1) pre-RADs } PSA
 } Gleason score
 } clinical stage
 } % of +ve Bx cores
- 2) post-RADs } PSA nadir level
 } time to PSA nadir
 } post-nadir PSA DT

What are the management options for locally advanced PCa?

- 1) Radical Prostatectomy + PLND
- 2) RADs + ADT
- 3) primary ADT
- 4) WW
- 5) clinical trials

RADICAL PROSTATECTOMY

Why has the use of RP for management of locally advanced PCa decreased?

- only 10% of men diagnosed with PCa present with locally advanced disease
- recognition that RP alone in these patients is often insufficient Rx
- improvements in EBRT delivery
- recognition that less-invasive multi-modal Rx (eg EBRT + hormones) has similar outcomes

How successful is RP for clinical stage T3 disease?

- 5yr overall survival is 64-96% and **PCa-specific survival is 85-92%**
- 10yr overall survival is 12.5-72% and **PCa-specific survival is 79-82%**
- 15yr overall survival is 20-51%
- **progression-free survival is ~40% at 10yrs**
- many men with clinical T3 disease have regional spread and may not benefit from RP
- select patients (eg lower volume disease) may benefit as local control may be achieved in most while complete cancer excision is possible in some
- ➔ **overall PSA-free survival after RP (w/o adjuvant Rx) in high-risk men is ~50% at 5-7yrs**

How successful is RP for pathological advanced disease?

- **men presenting with clinically advanced disease do slightly worse than men found to have pathologically advanced disease**
- majority of men found to have pathologically advanced disease post-RP were "high-risk" men pre-op based on PSA & Gleason score
- pT3a disease, SV involvement (pT3b), +ve margins, LN +ve disease associated with significantly higher biochemical recurrence rates
- 5yr clinical progression rate is 35% for pT3a disease (vs 7% for pT2 disease)

What is the role of NEOADJUVANT ADT prior to RP for locally advanced PCa?

- non-randomized studies have shown lower +ve margin rates & trends toward improved biochemical outcomes } clinical downstaging in 30-90% BUT pathologic downstaging less common (8-31%)
- **randomized, prospective trials show NO benefit of neoadjuvant ADT prior to RP**
- **could be used to ↓ size of prostate gland } makes RP technically easier** (less blood loss)
- no significant decrease in SV invasion or LN mets
- no improvement in PCa-specific survival or overall survival
- Soloway et al, J Urol '02 \ - RP + 3 months neoadjuvant ADT vs RP alone
- Klotz et al, J Urol '03 } - no significant difference in biochemical recurrence rate
- Aus et al, BJU Int '02 /
- Gleave et al, J Urol '03 } 8 vs 3 months neoadjuvant ADT
- } **may improve +ve margin rates**
- } no significant difference in PSA recurrence rate at 3yr interim analysis

What is the role of NEOADJUVANT CHEMO prior to RP for locally advanced PCa?

- studies have examined neoadjuvant chemo as well as combined neoadjuvant chemo + ADT
- Konety et al, J Urol '04 \ - **may see pathologic downstaging in ~30%**
- Pettaway et al, J Clin Oncol '00 } - **+ve margins seen in only ~20%**
- Clark et al, Urology '01 /

What are the benefits of adjuvant local or systemic therapy for PCa, as opposed to neoadjuvant Rx?

- 1) prevent delay in time to RadP
- 2) reduce operative morbidity
- 3) identify those men with adverse pathologic features or evidence of residual disease

What is the role of ADJUVANT RADs after RP for locally advanced PCa?

- usually **60-64 Gy to prostate bed** } advisable to wait 3-4 months after RP
- **Bolla et al, Lancet 2005 (EORTC)**
 - 1005 men randomized to adjuvant RADs vs surveillance
 - pT3, SV invasion, +ve margin
 - **improved biochemical progression-free survival & local progression**
 - **NO OVERALL SURVIVAL BENEFIT**
- **Thompson et al, JAMA '06 (SWOG)**
 - 425 men randomized to adjuvant RADs vs surveillance
 - pT3, SV invasion, +ve margin
 - **improved PSA relapse rate & disease recurrence rate**
 - TREND towards improved mets-free & overall survival } **UPDATE SHOWS BENEFIT !!!**
- criticisms } no evidence of overall survival benefit (changing!!!!)
- } no evidence that early RADs is better than salvage

What are the criticisms against adjuvant RADs post-RP?

- 1) not all patients with pT3 or +ve margins have local tumour recurrence
 - overtreating with RADs } overtreatment in 20% for pT3, 50% for +ve margins
 - may recur with distant mets not locally
- 2) no evidence to suggest adjuvant post-RP RADs is any better than early salvage RADs
 - adjuvant always look better due to bias (includes Rx of those that will never recur)

What is the role of ADJUVANT ADT after RP for locally advanced PCa?

- interest in adjuvant ADT comes from 2 sources
 - a) early ADT for biochemical recurrence post-RP beneficial over delayed (MRC & VACURG)
 - b) benefit of continued ADT after RADs (Bolla trial)
- few studies to date } **most show no significant benefit in overall survival**
- some show improvement in time to progression and PCa-specific survival (Prayer-Galetti et al, Eur Urol '00 → 25% improvement in PCa-free survival at 5yrs f/u)
- **BUT for LN+ve disease, early ADT shown to be better than delayed ADT** (Messing et al, NEJM '99 → 7yr survival improved from 65% to 85%)

RADIATION THERAPY

How successful is RADs for locally advanced, high-risk PCa?

- 5yr overall survival is 60-70%
- 5yr progression-free survival is <50% \ comparable to Rad P
- 10yr overall survival is <50% / (maybe slightly better)

What is the role of NEOADJUVANT ADT before RADs for locally advanced PCa?

- may reduce target volume and may potentially act as radio-sensitizer
- **appears to be appropriate in very high-risk patients**
- Pilepich et al, Int J Radiat Oncol Biol Phys '01
 - 471 men with cT2-4 tumours
 - randomized to RADs alone VS Zoladex + flutamide for 2mos before & during RADs
 - 4mos ADT associated with reduction in distant mets & improved local control
 - 4mos ADT had better PCa-specific survival & PSA-free survival
 - no difference in overall survival, although men with Gleason 6 seemed to have survival benefit

What is the role of ADJUVANT ADT after RADs for locally advanced PCa?

- **benefits those with very high risk disease**
- short period of ADT good for intermediate-risk PCa but more prolonged ADT better for high-risk PCa
- **Bolla et al, Lancet '02 (update of NEJM '97)**
 - only study to show overall survival benefit
 - 412 men with locally advanced PCa
 - randomized to RADs VS RADs + LHRH agonist for 3yrs (Zoladex)
 - median f/u 5.5 yrs
 - **significant improvement in disease-free & overall survival w/ adjuvant ADT**
 - 5yr overall survival was 78% (vs 62%)
 - 5yr disease-free survival was 74% (vs 40%)
 - 5yr PCa-specific survival was 94% (vs 79%)

What is the ideal dose and extent of RADs for locally advanced PCa?

- **doses >72Gy likely more effective**
- some studies to show whole-pelvis RADs better for progression-free survival but not overall survival
- HDR brachy + EBRT less well studied but may have a role

What is the role of CHEMO and RADs for locally advanced PCa?

- less well studied than RP and neoadjuvant chemo
- promising improvements that **require more study**

ADT AND ITS TIMING

What is the ideal time to start ADT for locally advanced PCa?

→ **early ADT shown to improve disease-progression and may also improve overall survival in men with more aggressive disease**

→ **need to balance benefits with effects of long-term ADT**

→ **VACURG studies**

- several studies examining different forms of ADT for locally advanced PCa
 - alternatives to estrogen should be used, given high cardiovascular toxicity
- early ADT shown to be beneficial } only in subset with more aggressive disease

→ **now with better PSA kinetics, delayed ADT may be just as good if we start delayed ADT at the right time**

→ **MRC study**

- early vs delayed ADT in 938 men with PCa (501 had locally advanced disease)
- improved PCa-specific mortality and overall survival in immediate ADT arm

→ **Kirk, Prostate Cancer Prostatic Dis '04 (MRC)**

- 934 men with locally advanced or asymptomatic metastatic disease
- randomized to immediate VS delayed ADT
- initially there was a survival advantage in immediate ADT arm, but on longer f/u the **overall survival was not significantly different**

- **PCa-specific death & symptomatic progression more common w/ delayed ADT**

→ **criticisms** } 6% of men in delayed arm died from PCa before receiving ADT

(no ADT is not the same as delayed ADT)

} 173 men were not staged (Mx) which could have impacted on randomization

} 10% in delayed group only got ADT once SC compression or pathologic fracture developed (?too late)

} no standardization of f/u protocol

What is the ideal timing of ADT in all-comers?

1) **low-risk, localized PCa**

→ **no overall survival benefit to immediate ADT**

→ **they likely do worse**

2) **locally advanced, asymptomatic mets, & clinically present but undefined PCa**

→ **immediate ADT results in significantly better PCa-specific survival**

BUT NOT overall survival

→ **must weigh PCa morbidity against S/Es of ADT**

3) **in N+ disease without primary treatment**

→ **there is no significant advantage to immediate ADT**

→ **1.6yr median survival advantage though (EORTC - Schroder)**

4) **in N+ disease after RP, there is a significant survival advantage to immediate ADT**

→ **2.6yr difference in median overall survival (ECOG - Messing)**

What is the role of anti-androgen monotherapy for locally advanced PCa?

- investigational
- no definitive studies

What is the role of intermittent ADT for locally advanced PCa?

- investigational
- no good studies

What is the QOL cost-benefit analysis for long-term adjuvant ADT + RADs?

- survival benefits of adjuvant ADT + RADs (short and long-term) for locally advanced PCa outweigh associated side effects in NNT analysis
- despite increased side effects associated with long term adjuvant ADT compared to short-term adjuvant ADT, this approach was better in almost all endpoints

MANAGEMENT OF DELAYED SEQUELAE

List some of the arguments for RP over RADs in locally advanced PCa

- 1) may influence survival in a subset of patients with high-risk PCa
→ small subset with locally advanced PCa may be cured with RadP
- 2) local recurrence after RADs may lead to the need for additional local treatment (eg TURP)
→ 10yr local recurrence rates after RADs for cT3 PCa range from 24-74%

What are some of the local complications of untreated local tumour progression?

- direct comparison of RP vs RADs for locally advanced PCa challenging
- even with neoadjuvant & adjuvant systemic therapy, leaving prostate in situ poses potential problems
- UTIs (80%)
- BOO (75%) } need for TURP (~30%)
- gross hematuria (45%)
- hydronephrosis and MUO (20-40%)
- incontinence
- rectal infiltration

CLINICAL TRIALS

Table 102-11 -- Current Phase III Clinical Trials in Locally Advanced/High-Risk Prostate Cancer

Study	Eligibility Criteria	Treatments
<i>Radical Prostatectomy</i>		
Neoadjuvant		
CALGB 90203	Clinically localized, ≤ 60% 5-year disease free	Surgery alone vs. estramustine and docetaxel
Adjuvant		
SWOG 9921	Gleason 8-10, pT3b-4, N+, Gleason 7 and + margin	AD (2 year) vs. AD + mitoxantrone and prednisone
RTOG 0011	Gleason ≥ 7 and PSA > 10ng/mL or + margin or pT3b, Gleason < 7 and 2 or 3 (PSA, margin, pT3b)	AD + RT vs. RT vs. AD (63-66Gy)
SWOG 8794	pT3 N0 M0	Observation vs. RT
EORTC 22911	pT3 N0	Observation vs. RT (60Gy)
<i>External Beam Radiation Therapy</i>		
Neoadjuvant		
RTOG 9910	Gleason 2-6 and PSA 10-100ng/mL, Gleason 7 and PSA < 20ng/mL, cT1 and Gleason 8-10 and PSA < 20	8 weeks NAD vs. 28 weeks NAD
Adjuvant		
RTOG 9902	Gleason ≥ 7 and PSA 20-100ng/mL, ≥ cT2 and Gleason ≥ 8 and PSA < 100ng/mL	AD vs. AD + estramustine, etoposide, and paclitaxel
EORTC 22961	cT1c-2b N1-2, cT2c-4 N0-2	6 months AD vs. 3 years AD
<i>Androgen Deprivation</i>		
CAN-NCIC-PR3	cT3-4 N0 M0, cT2 and PSA > 40ng/mL cT2 and PSA > 20ng/mL and Gleason ≥ 8	AD alone vs. additional pelvic RT
NCT 55731	Gleason > 7, cT3-4, N1 PSA > 20ng/mL	AD vs. AD + docetaxel and estramustine

Chapter #103 – Rising PSA after Definitive Local Therapy

WHEN DOES A PATIENT OCCUPY THE CLINICAL STATE OF A RISING PSA?

What are the 5 clinical states of recurrent PCa?

Clinical State	Rx Goals	Standard Rx Options
1) rising PSA + no mets + non-castrate T (biochemical recurrence)	prevent mets	→ salvage RADs → ADT (LHRH agonist)
2) mets + non-castrate T (clinical recurrence)	prolong life & reduce pain	→ ADT (CAB)
3) rising PSA + no mets + castrate T (biochemical HRPc)	prevent mets	→ no standard Rx → ?hormone manipulation
4) rising PSA + mets + castrate T (metastatic HRPc)	prolong life, reduce pain & prevent skeletal morbidity	→ CHEMO → bisphosphonates
5) CHEMO-refractory disease	palliate symptoms & prolong life	→ no standard Rx → mitoxantrone radiopharmaceuticals → palliative RADs

What are the 2 main issues when deciding on management of a rising PSA?

- 1) to determine whether the rising PSA represents local recurrence, systemic recurrence, or both
- 2) to distinguish between high-risk and low-risk patients and to determine the probability that a clinically significant event will occur (eg growth in primary site that can no longer be eliminated, detectable mets, or death from disease)

→ have to balance the need for therapy (based on what the cancer might do to the patient) with the decrement in QOL associated with therapy

What is the $T_{1/2}$ of PSA?

- 2-3days

What is the definition of the clinical state of rising PSA?

- biochemical failure after definitive local therapy
- no evidence of mets on standard imaging
- 2nd largest group of PCa patients (after those with localized disease)

What is the definition of biochemical failure post-RP?

- **rising PSA ≥ 0.4 ng/mL at >8weeks post-RP** \ very low levels of PSA can represent
- **ASTRO says PSA >0.5ng/mL** / benign glands at surgical margins
- exact level of PSA is moot point b/c single abN PSA does not mean clinically significant event

What is the definition of biochemical failure post-RADs?

- 1) ASTRO definition
 - **3 consecutive PSA rises, separated by 3 months between measurements**
 - starting >2yrs after initiation of radiation
 - time of failure back-dated to the midpoint between the nadir and the 1st confirmed rise
- 2) Phoenix criteria
 - **≥ 2 ng/mL rise in PSA above the post-RADs nadir**

IMAGING AND OTHER TESTS TO DETERMINE WHETHER RISING PSA SIGNIFIES LOCALIZED DISEASE, METASTATIC DISEASE, OR BOTH

What are the roles of bone scans & CT scans in patients with biochemical failure?

- **presence of overt clinical mets signifies patient is no longer in biochemical failure**
- **limited because unable to detect early metastatic disease**

- 1) bone scan } if kidneys not visualized, think false -ve scan
 } can't see lesions <0.4cm
 } trauma, infection, inflammation may be mistaken for mets
- 2) CT scan } unable to detect lesions <0.5cm
 } difficult to distinguish scar tissue or fibrosis from tumour

What other imaging modalities are being studied to distinguish localized recurrence from distant mets?

- all considered investigational
- 1) MRI with endorectal coil } can reveal sites of recurrent PCa near prostate bed & bladder
- 2) PET } may not be able to visualize all lesions
 } FDG-PET may help identify early bone mets, not seen on bone scans
 } FDG-PET may also help distinguish mets from nonmalignant uptake on bone scan
- 3) ProstaScint } **approved by FDA**
 } murine Ab (7E11) that targets PSMA found on N & malignant prostate cells
 → also taken up by gut, liver, kidney so not specific (**high false +ves**)
 } used to detect occult mets & when combined w/ MRI, may have better specificity

What is the role of prostate-bed Bx's post-RP?

- **if rising PSA + abN DRE or abN imaging suggestive of local recurrence, Bx is warranted**
 - +ve Bx revealing local disease may prompt salvage RADs or hormones
 - most patients will not have palpable lesions or evidence of local recurrence on imaging
- **yield of blind Bx's in the prostate bed are usually low**
 - also poorly predicts efficacy of salvage RADs because can't r/o concurrent mets

What is the role of prostate Bx post-RADs?

- **evidence of locally persistent disease after EBRT may lead to salvage therapy**
 - salvage RP
 - salvage cryotherapy
 - salvage brachytherapy
- risk of false +ve Bx findings declines after 2yrs from completion of EBRT
 - ie presene of PCa on Bx within first 2yrs may not represent persistent cancer

MODELS TO PREDICT LOCAL VS SYSTEMIC RECURRENCE AND TO PREDICT SURVIVAL

In a patient with a rising PSA post-RP, what features suggest local recurrence?

- 1) low Gleason grade
- 2) +ve margin } if margins +ve, may respond better to salvage RADs
- 3) no T3a, SV or LN involvement
- 4) PSA nadir reached undetectable levels
- 5) long interval between PSA nadir and biochemical recurrence (>2yrs)
- 6) **long PSA DT (>6-12 months, depending on study) during biochemical failure**
- 7) low PSA velocity (<0.75 ng/mL/yr)

What are the features suggestive of successful salvage RADs post-RP?

➔ **Katz et al, J Clin Oncol '03**

- +ve margins
- pT3a disease
- no SV invasion

➔ **Stephenson et al, Proc ASCO'03**

- +ve margins
- Gleason ≤ 7
- pre-salvage RADs PSA level < 2 ng/mL
- PSA DT > 10 months

➔ Ward et al, J Urol '04

- no SV invasion
- low Gleason grade
- low pre-salvage RADs PSA level
- PSA DT >12 months

What is the significance of PSA DT?

- **considered dominant factor used to assess the risk for development of mets-free survival**
→ short PSA DT likely means distant mets, not local recurrence
- **short PSA DT assoc'd w/ decreased overall & PCa-specific survival**
→ post-RADs AND post-RP
- no consensus, however, regarding the optimal # of PSA values that should be used, the time interval over which they should be determined, whether they need to be consecutive, and whether they should be separated by a minimum time
- another confounder is the effect of neoadjuvant or adjuvant ADT during radiation

TREATMENT STRATEGIES FOR RISING PSA

What are the main treatment options for biochemically recurrent PCa after local therapy?

- if believed to be local failure
 - 1) salvage RADs (minimum 64Gy as per ASTRO)
 - 2) salvage RadP
 - 3) investigational alternatives } salvage cryo, salvage brachy, salvage HIFU, etc
- if believed to be systemic
 - 1) ADT
 - 2) CHEMO, clinical trial

What is the PSA threshold for initiating salvage RADs in a patient with a rising PSA post-RP?

- ASTRO recommends trigger PSA of 1.5 ng/mL
- others suggest lower trigger } 0.6 ng/mL (Katz et al, J Clin Onc '03)
- } 1.1 ng/mL (Schild et al, Mayo Clin Proc '94)
- } 0.2 ng/mL (Walsh)

What are the factors predictive of a good response to salvage RADs post-RP?

- 1) long interval of undetectable PSA before biochemical recurrence (>2yrs)
- 2) **PSA DT >10months**
- 3) pre-salvage RADs PSA <2ng/mL
- 4) no LN mets
- 5) +ve margins } if margins +ve, may respond better to salvage RADs
- 6) low-grade PCa
- 7) no SV invasion

What is the ideal timing of ADT in a patient with biochemical recurrence?

→ **unknown**

→ **many randomized trials suggest early ADT may be better** } most studies involve ADT around time of RADs

- Pilepich et al, Int J Radiat Oncol Biol Phys '03
- Bolla et al, Lancet '02 (update)
- Wirth et al, J Urol '04
- D'Amico et al, JAMA '04
- Messing et al, Lancet '06 (update)

→ **ASCO practice guidelines (Loblaw et al, J Clin Oncol '04)**

- recommend initial observation with delayed ADT at time of clinical mets
- study pts above are different than pts w/ biochemical failure after primary local Rx
- no clinical data to demonstrate ADT at time of relapse improves survival over ADT applied at time of mets

What is the PSA threshold for initiating ADT in a patient with a rising PSA?

- some suggest 10 or 20 ng/mL } based on increasing risk of radiographic evidence of mets

→ **doesn't account for rate of PSA rise, Gleason score, or pretreatment PSA**, all of which predict time to mets, progression-free survival, and overall survival

Once hormones are started, what issues are important?

→ same controversies relating to hormone Rx in patients with clinical mets

- 1) what is the role of intermittent hormones?
- 2) Is CAB better than orchiectomy or LHRH monotherapy?
- 3) What is the role of high-dose bicalutamide in these patients? (shortens survival in patients w/ localized disease)
- 4) What is the role of bisphosphonates in preventing bone loss?

What are the overall recommendations on the timing of ADT for a rising PSA?

- 1) low-risk patients } unlikely to develop mets, symptoms, or death from PCa
→ observation +/- delayed ADT
- 2) intermediate-risk patients
→ early ADT
→ investigational approaches to slow disease to point where patient dies from other causes +/- delayed ADT
- 3) high-risk patients (eg PSA DT <6 months)
→ early ADT
→ clinical trial

What are the 3 phases of a clinical trial?

- phase 1 } define a dose and schedule
- phase 2 } seek evidence of a biologic or antitumour effect
- phase 3 } establish efficacy & safety compared to an established standard of care or placebo

What is the management of demonstrable disease in the prostate bed + a rising PSA?

→ **represents small proportion of patients**

→ **don't know if localized disease alone or localized disease + distant mets**

→ consider salvage RADs or ADT

- for local control, preservation of pelvic functionality, or disease eradication
- if estimated survival is longer than median duration of ADT (2yrs) then consider salvage RADs over ADT

What is the prognosis after biochemical recurrence post-RP?

- Pound et al JAMA '99

→ 1997 men post-RP (Walsh) } 15% biochemical recurrence (median time = 2yrs)

→ **8yrs from biochemical recurrence to soft tissue mets**

→ 2 more yrs until bone mets \

→ 2 more yrs until HRPcA }

→ 12-18months until death /

} time to death after mets is ~5yrs

→ biochemical recurrence precedes cancer-specific mortality by 13 – 13.5yrs

→ **time to development of mets predicted by:**

a) time to biochemical recurrence (> vs ≤2yrs)

b) Gleason score (5-7 vs 8-10)

c) PSA doubling time (≥ vs <10months)

→ time from RP to appearance of mets predictive of time until death

Chapter #104 – Hormone Therapy for PCa

HISTORICAL OVERVIEW OF HORMONE THERAPY

What was the seminal paper on androgen ablation and PCa?

- Charles Huggins & Clarence Hodges, Cancer Research '41 (U of Chicago)
 - castration of men with locally advanced & metastatic PCa
 - improvement in PAP levels
 - clinical improvement (eg bone pain, weight loss, etc)
 - first to describe the benefits of androgen blockade in the treatment of PCa
 - also recognized the existence of HRPc

What was the role of ESTROGENS in PCa?

- estradiol is 1000-fold more potent than T at **suppressing LH & FSH** by negative feedback
 - **also increases prolactin levels & SHBG levels**
- DES shown to be effective in PCa } get castrate levels of T (also pro-apoptotic)
- DES much cheaper BUT has high cardiovascular toxicity
- **NO LONGER USED DUE TO SIGNIFICANT CARDIOTOXICITY**

What is the role of GnRH ANALOGUES in PCa?

- 1) LHRH agonists } **initial surge in LH + T** release in response to agonist
 - } eventual loss of phasic pituitary stimulation results in decreased LH levels
 - } in absence of LH, testicular Leydig cells stop production of T
 - } eg Lupron, Zoladex
- 2) LHRH antagonists } loss of phasic pituitary stimulation resulting in decreased LH levels
 - } no agonist activity so **NO TESTOSTERONE FLAIR seen**
 - } eg Cetrorelix

What is the role of ANTI-ANDROGENS in PCa?

- bind to androgen receptor in a competitive fashion to inhibit androgen action
- 1) steroidal } binds to AR in nucleus and blocks activation
 - } also **decreases LH secretion by –ve feedback on pituitary** (progestational effect)
 - get loss of libido, ED
 - } eg cyproterone (Cyprostat/Androcur), megestrol
- 2) non-steroidal } binds to AR in nucleus and blocks activation
 - } **blocks testosterone feedback centrally**
 - results in paradoxically increased LH and T levels (serum levels are N)
 - } get **increased T** which is converted to estrogens peripherally
 - get gynecomastia, breast tenderness, etc
 - } prolonged use can lead to changes in the AR, leading to receptor activation
 - explains withdrawal effect seen after stoppage of anti-androgen
 - } eg **bicalutamide (Casodex), flutamide (Drogenil), nilutamide (Nilandron)**

MOLECULAR BIOLOGY OF ANDROGEN AXIS

What is the significance of the androgen receptor?

- **member of the nuclear receptor superfamily that includes:**
 - sex steroids (androgens, estrogens, progestin)
 - adrenal steroids (mineralocorticoids, glucocorticoids)
 - thyroid hormones
 - vitamin D
 - retinoids
- ligand-inducible transcription factor receptor
 - binding of T to AR induces transcription of target genes within the specific cell
- **all current forms of ADT work by reducing the ability of androgen to activate the AR**
 - a) lowering levels of circulating androgens**
 - b) blocking the binding of androgens**
- HRPC may therefore be a result of activation of androgen receptor-mediated pathways

Why is term “androgen independent PCa” a misnomer?

- even in HRPC, cancer is NOT resistant to androgens
 - 87% of patients w/ HRPC have symptomatic tumour flare when given exogenous androgens
- **should continue ADT even in HRPC**

What are the main classes of hormonal interventions for PCa?

- 1) castration } medical or surgical
 - eliminate production of T (95% from testes)
- 2) block binding of DHT to AR nucleus
- 3) prevent conversion of T to DHT

Drug Class	Site of Action	Mechanism of Action	Risks
- GnRH agonists eg Lupron	anterior pituitary	decreases LH release by down-regulation of GnRH receptor	testosterone surge
- GnRH antagonists eg Abarelix	anterior pituitary	directly inhibits GnRH receptor	anaphylaxis
- adrenal ablating drugs eg Ketoconazole	adrenal gland	decreases androgen synthesis from steroid precursors via inhibition of CYP450	steroid supplements needed to prevent adrenal insufficiency
- anti-androgens eg Casodex	prostate gland	inhibits androgen receptor via competitive binding	gynecomastia, increased LFTs, and mastodynia
- 5ARIs eg finasteride	prostate gland	decreases conversion of testosterone to DHT via inhibition of 5AR	no defined role in standard PCa mgt

SOURCES OF ANDROGEN

Describe the endocrinology of the prostate.

- hypothalamus makes GnRH (LHRH)
- LHRH stimulates pituitary to release LH
 - **LHRH agonists/antagonists block LH release from pituitary**
 - **steroidal anti-androgens can also block LH release from pituitary**
 - **non-steroidal anti-androgens block –ve feedback, so ↑ LH release from pituitary**
- LH stimulates Leydig cells in testis to make T
- T converted peripherally by aromatase into estrogens
 - **DES blocks LH & FSH release by negative feedback on pituitary**
- pituitary also releases ACTH
- ACTH stimulates adrenal gland to produce androstenedione
 - androstenedione can be converted peripherally into T (by 17 β -hydroxysteroid dehydrogenase)
 - **complete androgen blockade to block adrenal androgens**

What are the sources of androgen?

- 1) testes } T from Leydig cells account for 95% of circulating androgen (~6mg/day)
 - } **57% bound to SHBG, 40% bound to albumin, and 3% free (active form)**
 - tiny amount bound to transcortin, progesterone-binding globulin, α -acid protein
 - } converted to DHT in cell cytoplasm by 5AR
 - } DHT is 13x more potent than T
- 2) adrenal gland } **accounts for only 5% of T**
 - } relatively weak compared with T & DHT
 - } androstenedione & dehydroepiandrosterone (DHEA) production stimulated by ACTH made in pituitary
 - } adrenal androgens are almost entirely albumin-bound
 - } N levels after orchiectomy BUT are insufficient to maintain prostatic epithelium

Which androgens are made by the testis?

- testosterone
- androstenediol
- androstenedione (can't convert to DHT)
- DHEA
- DHT

Which androgens are made by the adrenals?

- testosterone
- androstenediol
- androstenedione (can't convert to DHT)
- DHEA
- DHEAS (**only made in adrenal**)
- progesterone

} stimulated by ACTH, NOT gonadotropins,
 } so orchiectomy will NOT change adrenal
 } androgens
 } → theory behind combined androgen blockade

Table 104-1 -- Major Circulating Androgens

Source	Androgen	Amount Produced per Day (mg)	Relative Potency	Relative Potency/Amount Produced
Testes	Testosterone	6.6	100	15.2
Testes and peripheral tissues	Dihydrotestosterone	0.3	160–190	533–633
Adrenal	Androstenedione	1.4	39	27.9
Adrenal	Dehydroepiandrosterone	29	15	0.5

MECHANISMS OF ANDROGEN AXIS BLOCKADE

What are the 4 main therapeutic approaches for androgen blockade in PCa?

- 1) ablation of androgen sources } eg orchiectomy
- 2) anti-androgens } eg casodex (bicalutamide), cyproterone acetate
- 3) inhibition of LHRH or LH release } eg Lupron (leuprolide), Zoladex (goserelin), DES
- 4) inhibition of androgen synthesis } eg ketoconazole, aminoglutethimide

Table 104-2 -- Therapeutic Approaches to Androgen Deprivation Therapy[*]

Ablation of Androgen Sources	Inhibition of Androgen Synthesis	Antiandrogens	Inhibition of LHRH or LH
Orchiectomy	Aminoglutethimide	Cyproterone acetate	DES
	Ketoconazole		Leuprolide
		Flutamide	Goserelin
		Bicalutamide	Triptorelin
		Nilutamide	Histrelin
			Cetorelix
			Abarelix

How effective is orchiectomy?

- **fastest way to get circulating T levels to <50 ng/dL (castrate range)**
- **T levels reduced by >90% within 24hrs } testosterone T_{1/2} = 20-30 minutes**
- simple complete orchiectomy VS subcapsular orchiectomy
 - avoids psychological consequences of empty scrotum
 - if properly performed, has same hormonal & cancer response as complete orchiectomy

What are the advantages of medical castration over surgical castration?

- 1) no need for surgery
- 2) possible to reverse
- 3) cosmesis
- 4) easier to manage hot flashes & loss of libido

What are the pros & cons of surgical castration?

PROS	CONS
<ul style="list-style-type: none"> - induces almost immediate castrate levels of T - low cost - compliance not an issue - effective 	<ul style="list-style-type: none"> - irreversible - surgical procedure - cosmesis/body image - irreversible loss of libido - hot flashes much harder to Rx

What are the side effects of ADT?

Early	Late
Flare phenomenon	Osteoporosis, fractures
ED	Personality changes, depression, ↓ mental acuity, ↓ concentration
Hot flashes	Weight gain
Gynecomastia, breast tenderness	↓ muscle mass
Cardiovascular	↓ physical activity
Liver failure	Anemia
Adrenocortical insufficiency	Change in lipid profile
Glucose intolerance	↓ QOL
Appetite changes	Androgen independence

How effective are **STEROIDAL ANTI-ANDROGENS**?

→ cyproterone acetate (Androcur) 100mg po bid/tid

1) **direct androgen receptor blocker**

2) **also get central –ve feedback on pituitary LH secretion** } progestational effects of steroidal

→ **results in hypogonadal state**

→ rapidly lowers T levels to 70-80%

- **side effects** } loss of libido

} ED (80%)

} decreased energy

} **severe cardiovascular complications in up to 10% (MI/DVT/PE)**

} **gynecomastia in <20% (mastodynia less common)**

} fluid retention

} **liver toxicity (may be serious)**

How effective are **NON- STEROIDAL ANTI-ANDROGENS**?

→ flutamide (250mg tid), bicalutamide (50mg od), nilutamide (150mg od) } pure anti-androgen

1) **blocks androgen receptor**

2) **also blocks testosterone feedback centrally**

→ **results in increased LH & T levels** } **no hypogonadal state**

→ ?better libido and less ED

→ monotherapy does not induce osteoporosis

- peripheral aromatization of increased T leads to **↑'d estradiol levels** } get many side effects

- **side effects** } gynecomastia common

} mastodynia

} **diarrhea (flutamide)**

} **visual disturbances & interstitial pneumonitis (nilutamide)**

} liver toxicity (may be serious)

What are the advantages & disadvantages of the different non-steroidal anti-androgens?

	ADVANTAGES	DISADVANTAGES
1) flutamide 250mg TID	- maintains testosterone levels - no fluid retention	- short $T_{1/2}$ (6hrs) so requires TID dosing - renal clearance - ++ diarrhea, increased LFTs - shorter overall survival (as monotherapy) compared to DES
2) bicalutamide 50mg OD	- long $T_{1/2}$ (6days) so OD dosing - most potent non-steroidal anti-androgen - best tolerated - maintains T levels	- as 50mg monotherapy, survival is inferior to castration in men with PCa mets (equivalent if 150 mg OD) - gynecomastia & hot flashes - worse overall survival cf WW in men with low-risk, localized Pca
3) nilutamide 150mg OD	- long $T_{1/2}$ (56hrs) so can have OD dosing (BUT needs loading for 1 month at 300mg od)	- 25% have visual problems (delay in light to dark adaptation) - 1% get interstitial pneumonitis that can progress to pulmonary fibrosis

What is the anti-androgen withdrawal phenomenon?

→ drop in PSA level after withdrawal of anti-androgen from CAB

- may be due to mutations in the AR that have made anti-androgen act like an agonist

→ LNCaP receptor mutation

- seen within 6weeks of casodex withdrawal

- **15-30% have PSA declines of >50% after withdrawal**

→ also see symptomatic benefits, and rarely, improvements in soft tissue & bone mets

→ **median duration of only 3.5 to 5 months**

- no increase in overall survival in men demonstrating anti-androgen withdrawal phenomenon

How effective are **LHRH AGONISTS**?

- Lupron (leuprolide) 7.5mg/22.5mg/30mg IM (1, 3, and 4 month depots)
 - Eligard is same dosages but SC administration
- Zoladex (goserelin) 3.6mg/10.8mg SC (1 and 3 month depots)
- Suprefact (buserelin) 9.9mg SC (3 month depot)
- Trelstar (triptorelin) 3.75mg/11.25mg IM (1 and 3 month depots)
- Vantas (histrelin) 50mg SC (1 yr depot)
- 1) **decreases LH release by down-regulation of GnRH receptor (pituitary)**
 - different agonists differ at position 6 in the peptide
 - **LH & T flare may last up to 20days**
 - can result in severe, life-threatening exacerbation of symptoms
 - **need co-administration of anti-androgen for ~4wks**
 - shown to have survival equivalent to that of orchiectomy
 - castrate levels by ~1 month } **decreases T levels but DOES NOT affect DHEAS levels**
 - **side effects** } hot flashes (46%)
 - } gynecomastia & mastodynia
 - } ED & decreased libido (common)
 - } increased lipid profile
 - } fatigue & depression
 - } dizziness & headache
 - } anemia

How effective are **LHRH ANTAGONISTS**?

- Plenaxis (abarelix), Cetrotide (cetrotorelin) 1mg sc od (new generation with less allergic response)
- 1) **binds competitively to LHRH receptors in pituitary**
 - reducing LH levels by 84% within 24hrs of administration
 - **no LH & T flare so no need for anti-androgen co-administration**
 - good for those with large tumour burden, in whom this could be real problem
 - equivalent to LHRH agonist + anti-androgen in achieving castrate levels of T
 - **side effects** } **severe allergic reactions (even after previous uneventful Rx)**
 - } gynecomastia & mastodynia
 - } LUTS
 - } fatigue

How effective is **KETOCONAZOLE**?

- Nizoral 400mg po tid
- 1) azole antifungal agent that interferes with two CYP450 dependent pathways
 - **get loss of T synthesis by Leydig cells & steroid synthesis in adrenals**
 - **inhibits 17, 20 desmolase**
 - T levels drop to castrate levels within 4-48hrs of administration
 - **fastest medical way to reach castrate levels (eg acute SC compression)**
 - effects are immediately reversible } benefit over bilateral orchiectomy
 - no good for long-term therapy } T levels being to rise towards low-N ranges w/in 5 months
 - **get adrenal suppression so need to give with hydrocortisone 20mg bid**
 - **side effects** } gynecomastia
 - } lethargy & weakness
 - } **hepatotoxicity**
 - } **visual disturbances**
 - } nausea
 - } ED
 - } **adrenal insufficiency**
 - } increases coumadin levels
 - } H/A
 - } skin rash
 - } **thrombocytopenia**
 - } increased TG's

How effective is aminoglutethimide?

→ 1g po od

1) inhibits conversion of cholesterol to pregnenolone

→ **blocks steroidogenesis by inhibiting StAR**

→ **blocks adrenal androgen synthesis but ALSO blocks production of aldosterone and cortisol } medical total adrenalectomy**

→ **requires replacement of cortisone & fludrocortisone**

- ~40% get a >50% decrease in PSA levels } median response time lasting 9 months

- **side effects** } anorexia & nausea

} skin rash

} **lethargy & somnolence (35-40%)**

} vertigo & nystagmus

} hypoT4

} **adrenocortical insufficiency**

} **hypoaldosteronism w/ orthostatic hypoTN**

How effective is **ESTROGEN (DES)**?

1) **suppresses T production by –ve feedback on hypothalamus** } get ↓'d LH & FSH

2) may also have **pro-apoptotic effect on PCa cells (cytotoxic)**

3) **↑'s SHBG & prolactin** and thereby decreases free T levels

- see castrate levels of T in 2-4wks

- side effects } **CAD/MI/CVA/DVT/PE**

} breast Ca & ovarian Ca risk

} ED & loss of libido

} hot flashes

} gynecomastia

→ **no longer used due to excessive mortality from CVS S/Es** } **lower risk w/ transdermal**

What is PC-SPES?

- herbal dietary supplement } **estrogen action** + **5ARI action** + anti-mutagenic activity

} contains estrogen & warfarin

What is the time to plasma testosterone nadir in surgical & medical castration?

1) **simple orchiectomy** } **>90% reduction within 24hrs**

→ **mean ~ 9hrs (fastest way to reach castrate levels)**

2) LHRH agonists (eg Lupron) } 2-4weeks (+ flare)

3) LHRH antagonists (eg Abiraterone) } 2 weeks (no flare)

4) Estrogen (eg DES 3mg) } 38days

5) **ketoconazole** } **4-48hrs (fastest form of medical castration)**

→ anti-androgens maintain N testosterone levels

What are the ABCs of ADT complications?

A – anemia

I – increased lipids

B – bone loss & fractures

J, K

C – cognitive decline

L – loss of muscle mass

D – depression

M – metabolic syndrome

E – ED

N – no libido

F – fatigue

O – obesity

G – gynecomastia

P – personality changes

H – hot flashes

List the hormonal effects of pure androgen antagonists (non-steroidal).

- ↑'d testosterone

- ↑'d LFTs

- ↑'d LH

- ↑'d estradiol

- ↑'d FSH (only flutamide)

- ↑'d T bili

COMPLICATIONS OF ANDROGEN ABLATION

What are the common side effects of androgen ablation?

- 1) osteoporosis } >50% of men meet criteria for osteopenia or osteoporosis even before ADT
→ >2.5 standard deviations below age-specific mean
} 4yrs of ADT puts average man in osteopenia range
} cumulative risk of fractures almost 2-fold higher if on ADT
Rx → initial BMD + periodic BMD tests to assess bone health
→ **weight-bearing exercise, smoking cessation, wt loss, decrease EtOH**
→ **Vit D, calcium, consider estrogen**
→ **bisphosphonates**
 - BMD increases in men on ADT if on zoledronic acid (Zometa)
 - Zometa also delays time to 1st skeletal-related event (SRE) by 5-6months and total SREs (**Saad et al, JNCI '02**) in men w/ advanced PCa and PCa with bone mets
- 2) **hot flashes** } **occurs in 50-80% on ADT** but generally decreases in frequency & intensity
} treatment based on degree of bother
Rx → **1st line is megestrol acetate (progestin) 5-20mg bid** } **s/e hyperphagia**
→ **2nd line is venlafaxine (SNRI) 12.5mg bid** } >50% get reduced symptoms
→ cyproterone acetate 50-300mg od (steroidal anti-androgen) } high risk of DVT/PE
→ **transdermal estradiol patch** } **most effective treatment BUT** painful gynecomastia & DVT/PE common
→ clonidine (α -agonist) } mixed results
- 3) sexual dysfunction (ED & loss of libido) } very common but not inevitable
→ 20% maintain some sexual activity
} ED in ~85%
} decreased libido more common (95%)
Rx → very difficult, especially for libido issues
- 4) cognitive effects } increased memory loss, depression, and overall cognitive decline
- 5) changes in body habitus } loss of muscle mass & increase in % of fat body mass common
→ overall increase in weight due to fat mass
- 6) gynecomastia } more common after non-steroidal anti-androgens (Casodex) and DES
} may also get breast tenderness
Rx → prophylactic RADs (10Gy) used to prevent painful gynecomastia
 - no benefit once gynecomastia has begun→ SERMs (tamoxifen), switch to steroidal anti-androgens
- 7) anemia } common even in men without bone mets (normocytic)
} 90% on combined ADT get \geq 10% drop in Hgb
} due to lack of T stimulation of erythroid precursors & decrease in epo production
} associated with shorter survival in those anemic before starting ADT
Rx → epo } reversible after stopping ADT (may take up to 1yr)
- 8) metabolic syndrome } elevated BS, HTN, elevated cholesterol, increased obesity
→ increased incidence of CVD and DM

List 3 hormonal & 3 non-hormonal meds used for hot-flashes in men on ADT

→ “Each Capsule Gonna Cool Me Down”

→ Non-hormonal

- 1) Effexor/venlafaxine (SNRI) 12.5mg po bid } **SECOND LINE**
- 2) Clonidine
- 3) Gabapentin

→ Hormonal

- 1) Cyproterone acetate (steroidal anti-androgen) 50-300mg od } high risk of DVT/PE
- 2) **Megestrol acetate (progestin) 5-20mg bid** } **FIRST LINE**
- 3) **DES/estradiol patch** } most effective Rx BUT painful gynecomastia + DVT/PE common

How does ADT lead to osteoporosis?

- lack of T results in lack of osteoblastic cell proliferation
- lack of T results in a failure of osteoclastic inhibition (via IL-6)

How does male osteoporosis usually present?

- usually very different than women
- later onset, more gradual onset } occurs more rapidly in men on ADT
- height loss
- kyphosis
- bone fractures
- back pain

What are the RFs for osteoporosis?

- Family Hx
- T deficiency (eg ADAM/SLOH)
- glucocorticoid excess
- hyperT4
- hyperPTH'ism
- Vit D deficiency
- excessive EtOH
- smoking
- GI disease
- COPD
- cancer
- meds } SSRIs, anti-convulsants, chemo, ADT

List the management options for osteoporosis prevention & treatment in men on ADT

→ prevention

- lifestyle modifications } weight loss, wt-bearing exercise, avoid excessive EtOH, stop smoking
- Ca supplements (800-1000 mg od)
- Vit D supplements (800-1000 IU od)

→ treatment

- anti-resorptive meds ("BET")
 - Bisphosphonates } binds to hydroxyapatite crystal in bone and reduces osteoclastic activity (bone resorption)
 - } iv zoledronic acid (Zometa 4mg q3months)
 - } po alendronate (Fosamax 70mg q1wk)
 - Estrogen patch/SERMs
 - Testosterone
- bone stimulating agents
 - Teriparatide } PTH-like agent that stimulates osteoblastic activity (bone formation)
 - Na fluoride

List the main side effects of bisphosphonates.

- oral } esophagitis, esophageal ulcers
- iv } flu-like symptoms (arthralgia, myalgia), hypoCa, hypoMg, nephrotoxicity, osteonecrosis of jaw

RESPONSE TO ANDROGEN BLOCKADE

What are the predictors of response to androgen blockade?

- 1) rate of PSA decline } >80% drop w/in 1 month predicts longer disease-free progression rate
 - incomplete or sluggish response is evidence of significant HRPCa
- 2) nadir PSA } nadir level predicts progression-free interval
 - **likely most important predictor**
- 3) pre-treatment T level } if T already low prior to initiation, response not as good
- 4) pre-treatment PSA } rapid rise before ADT associated with worse PCa-specific mortality
- 5) Gleason grade } higher grades associated with increased likelihood to progress on to HRPC
 - rise in PSA (evidence of HRPC) precedes bone mets by several months (~7months)

COMBINATION THERAPY

What is the theoretical advantage of CAB?

- adding anti-androgen will **eliminate effect of adrenal androgens** on PCa progression
- serum T does not drop to zero after medical/surgical castration } adrenal androgens driven by ACTH

What is the role of CAB in PCa?

→ **few studies demonstrating benefit**

- Crawford et al, NEJM '89
 - men with metastatic PCa
 - flutamide (250mg tid) + leuprolide (daily) VS leuprolide (daily) alone
 - CAB associated with significantly longer progression-free survival & overall survival
 - most benefit in men w/ "minimal mets" (no skull, ribs, long bones soft tissue)
- Dijkman et al, J Urol '97
 - orchiectomy + nilutamide VS orchiectomy alone
 - CAB had significantly longer median time to progression and higher overall survival

→ **some randomized studies show no significant survival advantage for CAB**

- Eisenberger et al, NEJM '98
 - 1387 men with metastatic PCa
 - randomized to bilateral orchiectomy alone VS bilateral orchiectomy + flutamide
 - no survival advantage w/ CAB for metastatic PCa } for extensive & minimal disease

→ **some studies uncertain**

- Prostate Cancer Trialists' Collaborative Group, Lancet '00
 - meta-analysis of 27 prospective, randomized clinical trials of CAB
 - 88% had metastatic disease
 - 20% died of causes other than PCa } not everyone with PCa mets died of PCa
 - 5yr overall survival was 2.9% better for CAB (27.6% vs 24.7%) when excluding studies with cyproterone acetate (steroidal)
 - **significant survival advantage of ~3% with CAB**
 - **BUT, meta-analysis had 0-5% range of uncertainty re: true size of benefit**

What is the role of NEOADJUVANT ADT prior to RP?

→ non-randomized studies have shown **lower +ve margin rates** & trends toward improved biochemical outcome } clinical downstaging in 30-90% BUT **pathologic downstaging much less common (8-31%)**

→ randomized, prospective trials show **NO BENEFIT of neoadjuvant ADT prior to RP**

→ **could be used to ↓ size of prostate gland } ?makes RP technically easier** (less blood loss)

→ no significant decrease in SV invasion or LN mets

→ no improvement in PCa-specific survival or overall survival

- Soloway et al, J Urol '02 \ - RP + 3 months neoadjuvant ADT vs RP alone
- Klotz et al, J Urol '03 } - no significant difference in biochemical recurrence rate
- Aus et al, BJU Int '02 /
- Gleave et al, J Urol '03 } 8 vs 3 months neoadjuvant ADT
 - } may improve +ve margin rates
 - } no significant difference in biochemical recurrence rate at 3yr interim analysis

What is the role of ADT in combination with EBRT?

- ↑'d overall survival, PCa-specific survival, & disease-free progression w/ adjuvant ADT
- benefit mainly in men with locally advanced disease or high-grade, high-risk disease
- maybe even in intermediate risk BUT NOT FOR LOW RISK
- optimal timing & duration of ADT is undefined

→ **Bolla et al, NEJM '97**

- 401 men with locally advanced PCa } prospective, randomized
- ~80% of men had T3 disease
- randomized to RADs vs RADs + LHRH agonist x3yrs (Zoladex)
- **overall survival at 5yrs better for RADs + hormones } 78% vs 62%**
- disease-free survival at 5yrs better for RADs + hormones } 85% vs 48%
- 5yr local control rate better for RADs + hormones } 97% vs 77%
- progression rates higher for RADs alone

→ **Bolla et al, Lancet '02 (update of NEJM '97)**

- 412 men with locally advanced PCa
- median f/u 5.5 yrs
- significant improvement in overall survival & disease-free survival with adjuvant ADT
 - 5yr overall survival was 78% (vs 62%)
 - 5yr disease-free survival was 74% (vs 40%)
 - 5yr PCa-specific survival was 94% (vs 79%)

→ **D'Amico et al JAMA '04**

- RCT OF 206 men } EBRT vs EBRT + ADT for intermediate & high risk localized PCa
- median f/u of 4.5yrs
- 6 months of Lupron/Zoladex had overall survival benefit at 5yrs (88% vs 78%)
- improved outcomes seen mainly in intermediate risk group

TIMING OF THERAPY

What are the indications for ADT in PCa?

- 1) Neoadjuvant/Adjuvant therapy with EBRT for high-risk PCa
- 2) adjuvant therapy for N+ PCa after RP
- 3) salvage treatment following failure of local therapy (post-RP, post-RADs)
- 4) primary therapy for metastatic PCa
- 5) HRPC (should always be continued)
- 6) primary therapy for localized PCa (an alternative Rx for older men, sick men, etc)

What are some important facts to consider when determining the timing of ADT?

- 1) natural hx of PCa progression is very protracted
 - Pound et al, JAMA '99 } 304 post-RP men
 - } median time from biochemical recurrence to soft tissue mets = 8yrs
 - } median time from mets to death = 5yrs
 - 2 yrs until bone mets, then another 2yrs until HRPC, then 1yr until death
 - Freedland et al, JAMA '05 } update on Pound data
 - } median time to PCa-specific death not reached after 16yrs of F/U
- **even without ADT, men with progressive PCa live for a long time**
- 2) despite dramatic clinical responses, men undergoing ADT either die of a non-PCa cause (20% based on CAB meta-analysis) or will develop HRPC and die of PCa
- 3) ADT is not innocuous and has many side effects affecting quality AND quantity of life
 - **metabolic syndrome becoming more common as ADT becomes more widely used**
- 4) timing issue of ADT is not new
 - studies during 70's showed no benefit of early ADT in men w/ locally advanced disease or mets
- 5) **there is no question that early ADT delays biochemical & clinical disease progression, BUT the effects of early ADT on survival remain unclear**

Localized PCa

What evidence exists AGAINST early ADT for low-risk PCa?

- Casodex Early PCa program (Iversen et al, Urology '04)
 - men randomized to casodex 150mg OD VS placebo, in addition to standard care
 - endpoints were overall survival, progression-free survival, and tolerability
 - in subset of M w/ clinically localized disease, overall survival significantly WORSE in ADT arm
 - increased non-PCa death in ADT arm
 - but used 150mg dose

Locally Advanced & Asymptomatic Metastatic PCa

What is the ideal timing of ADT for locally advanced or asymptomatic metastatic PCa?

- **Kirk, Prostate Cancer Prostatic Dis '04 (MRC)**
 - 934 men with locally advanced or asymptomatic metastatic disease
 - randomized to immediate VS delayed ADT
 - initially there was a survival advantage in immediate ADT arm, but on longer f/u the **overall survival was not significantly different**
 - **PCa-specific death & symptomatic progression more common w/ delayed ADT**
- **criticisms** } 6% of M in delayed arm died from PCa before receiving ADT (no ADT is not same as delayed ADT)
 - } 173 men were not staged (MX) which could have impacted on randomization
 - } 10% in delayed group only got ADT once SC compression or pathologic fractures developed (?too late)
 - } no standardization of f/u protocol

LN+ Metastatic PCa

What is the ideal timing of ADT for LN +ve PCa?

1) EARLY ADT

- **Messing et al, NEJM '99 (ECOG)**
 - 98 men with N1 PCa (post-RP) } 7.1yrs median f/u
 - randomized to immediate VS delayed ADT (if mets or symptomatic recurrence)
 - Zoladex or bilateral orchiectomy
 - overall survival, PCa-specific survival, recurrence rate better in immediate ADT arm
- **Messing et al, Lancet Oncol '06 (update)**
 - 11.9yrs median f/u
 - overall survival (64% vs 45%) better in immediate ADT arm } 2.6yr difference
 - PCa-specific survival & progression-free survival also better in immediate ADT arm
 - BUT, proportionately more non-PCa deaths in immediate ADT arm (55% vs 11%)
- **criticisms** } small study (risk of type 1 error)
 - } Gleason grading not centralized & there was no correlation between grade & survival (imbalance in randomization may exist)
 - } progression & PCa death in delayed ADT arm much more rapid than expected from other studies with N+ patients

2) DELAYED ADT

- **Schroder et al, J Urol '04 (EORTC)**
 - 302 men with pN1-3, Mo PCa (NO LOCAL TREATMENT) } 8.7yrs median f/u
 - randomized to immediate VS delayed ADT
 - LHRH agonist + 1 month antiandrogen or bilateral orchiectomy
 - no significant difference in overall survival (38.3% vs 39.5% immediate) or PCa-specific death (76.1% vs 76.2% immediate)
- **criticisms** } no treatment of primary tumour
 - } 1.6yr worse median survival in delayed ADT but 1.8yr benefit of being off ADT

*** **quantity of life gained with immediate ADT vs quality of life gained by delayed ADT** ***

What is the ideal timing of ADT in all-comers?

- 1) **low-risk, localized PCa**
 - no overall survival benefit to immediate ADT } they likely do worse
- 2) **locally advanced, asymptomatic mets, & clinically present but undefined PCa**
 - immediate ADT get significantly better PCa-specific survival BUT NOT overall survival
 - **need to weigh risk of PCa vs risk of ADT as well as quantity vs quality of life**
- 3) **in N+ disease without primary treatment**
 - there is no significant advantage to immediate ADT
 - 1.6yr median survival advantage VS 1.8yrs more of ADT
- 4) **in N+ disease after RP**
 - there is a significant survival advantage to immediate ADT
 - 2.6yr difference in median overall survival

What are the treatment options for HRPcCa?

- always measure T and ensure castrate levels
- 1) WW
- 2) hormonal manipulation
 - add anti-androgen (CAB)
 - stop anti-androgen (withdrawal effect if on CAB)
 - switch anti-androgen (if on CAB)
- 3) 2nd line hormone Rx ("SKATE Man")
 - Steroids
 - Ketoconazole
 - Aminoglutethimide
 - Tamoxifen
 - Estrogen (DES) + coumadin or ASA
 - Megestrol
- 4) CHEMO
 - **docetaxel } only option with CLEAR SURVIVAL BENEFIT (2.5 months) and CLEAR BENEFIT WITH SYMPTOMS**
- 5) clinical trial
 - eg Dendritic cell therapy (Provenge), etc

ECONOMIC CONSIDERATIONS

What is the most economic form of ADT?

- DES } cheapest form of ADT, particularly at 1mg od
 - NOT USED DUE TO RISK OF CARDIOVASCULAR COMPLICATIONS
- orchiectomy } more cost effective than LHRH agonists if >1 dose of 3month depot is needed
 - } LHRH agonists have no survival advantage over orchiectomy
- combined ADT } most expensive form of ADT
 - } no significant benefit over orchiectomy alone
 - } most cost-effective if initiated AFTER pts become symptomatic from mets

What are the disadvantages of surgical castration?

- irreversible
- psychologic effect of empty scrotum
- irreversible loss of libido
- hot flashes more difficult to control than medical castration
- CLEARLY CHEAPER AND JUST AS EFFECTIVE (IF NOT MORE)

THE FUTURE OF HORMONE THERAPY

Why is there interest in intermittent ADT?

- 1) intermittent androgen deprivation lengthened the time to emergence of androgen-refractory cancer growth in animal models (using Shionogi breast cancer tumour and LNCaP prostate cancer tumour)
- 2) debilitating side effects of continuous ADT

Why is intermittent ADT not considered standard treatment yet?

→ awaiting large RCTs

- 1) no evidence that intermittent ADT will delay emergence of HRPC in humans
- 2) return of normal androgen levels could actually accelerate PCa progression

Chapter #105 – HRPC

CLINICAL CONSIDERATIONS

How successful is ADT for metastatic PCa?

- **progression-free survival is ~12-20 months** \ one of the most effective systemic
- **overall survival is ~2-3yrs** / palliative Rxs for solid tumours
- **recent studies show longer survival times** } likely related to lead-time bias
- almost all patients develop HRPC

What is the definition of HRPC?

- 1) **3 consecutive rises in PSA in man with castrate level T over ≥1 month**
- 2) **evidence of new metastatic disease**

What molecular changes occur with the development of HRPC?

- 1) apoptosis is exceeded by cell proliferation
 - androgen ablation primarily increases apoptosis
 - **with HRPC, threshold for cell death ↑'s until proliferation exceeds apoptosis**
 - 2) **somatic alterations of the androgen receptor**
 - AR can be activated by other ligands such as estrogen & progestational agents
 - can also be activated in non-ligand manner by growth factors & cytokines
- **AR may be reasonable target for future Rx of HRPC**

What are the proposed mechanisms of androgen insensitivity?

- upregulation of survival genes
- amplification of AR gene
- AR mutation
- activation of alternate GF pathways
- clonal selection
- hypersensitivity of AR gene
- coactivators

Why is conventional cytotoxic CHEMO not a good primary therapy for PCa?

- proliferation rate of PCa cells is relatively slow compared to other common tumours (eg testis GCTs, lymphoma, small cell lung Ca)
- proliferation rate appears to increase after development of HRPC
- **CHEMO may have better results in HRPC, when cells have high growth fraction**

What are the 5 clinical states of recurrent PCa? (2007 AUA Update #38)

Clinical State	Rx Goals	Standard Rx Options
1) rising PSA + no mets + non-castrate T (biochemical recurrence)	prevent mets	→ salvage RADs → ADT (LHRH agonist)
2) mets + non-castrate T (clinical recurrence)	prolong life & reduce pain	→ ADT (CAB)
3) rising PSA + no mets + castrate T (biochemical HRPc)	prevent mets	→ no standard Rx → ?hormone manipulation
4) rising PSA + mets + castrate T (metastatic HRPc)	prolong life, reduce pain & prevent skeletal morbidity	→ CHEMO → bisphosphonates
5) CHEMO-refractory disease	palliate symptoms & prolong life	→ no standard Rx → mitoxantrone radiopharmaceuticals → palliative RADs

What is involved in the initial evaluation of a patient with HRPC?

- 1) history and P/E } symptoms, response to prior endocrine Rx, etc
- 2) PSA
- 3) serum testosterone (ensure castrate levels)
- 4) bone scan

What are the main factors to consider when deciding on Rx of HRPC?

- 1) extent of disease
- 2) mode & site of progression } biochemical (PSA relapse alone) VS clinical (new bone mets, visceral and nodal mets, presence of symptoms)
- 3) response to prior hormone therapy
- 4) PSA and testosterone hx } PSA DT, PSA velocity, testosterone levels

What is the prognosis once HRPC develops? (CHART)

- PSA relapse only } ~3yrs if minimal disease; ~1.5yrs if extensive disease
- PSA relapse & bone scan +ve } ~2yrs if minimal disease; ~1yr if extensive disease
→ decreases survival by ~1/3

What is the role of ADT in HRPC prior to initiating CHEMO?

- **CONTROVERSIAL**
- some evidence suggests stopping 4wks prior makes no difference, others show benefit of continuing ADT
- **likely better to continue ADT throughout any further Rx**

What is the role of anti-androgen withdrawal in HRPC?

- discontinuation of anti-androgens (both types) can result in short-term clinical responses
 - 15-30% have PSA decline of >50%
 - **median duration of only 3.5 to 5 months**
 - also see symptomatic benefits, and rarely, improvements in soft tissue & bone mets
- discontinuation of anti-androgen if on CAB is recommended prior to starting next therapeutic option
 - “withdrawal effect”
- **no overall survival benefit**

What are the options for HRPc?

- always measure T and ensure castrate levels
- 1) hormonal manipulation
 - add anti-androgen (CAB)
 - stop anti-androgen (withdrawal effect if on CAB)
 - switch anti-androgen (if on CAB)
- 2) 2nd line hormone Rx } “SKATE Man”
 - Steroids
 - Ketoconazole
 - Aminoglutethimide
 - Tamoxifen
 - Estrogen (DES + coumadin)
 - Megestrol
 - response rates range from 20-60%
 - response duration is usually very short (2-4months)
 - **may be good option for asymptomatic patients w/ limited metastatic disease, given potentially higher toxicity profile of chemo**
- 3) chemo
 - **eg docetaxel**
 - only option with CLEAR SURVIVAL BENEFIT (2.5 months) & CLEAR BENEFIT WITH SYMPTOMS
- 4) clinical trial
 - eg dendritic cell therapy (Provenge), etc

What features suggest consideration of more aggressive management of HRPC?

→ ie consider early CEMO

- 1) symptomatic disease
- 2) extensive mets
- 3) unfavorable PSA kinetics

→ PSA DT <3months associated with poor survival & early development of bone mets

- 4) pathology

→ high Gleason, anaplastic or neuroendocrine tumours less likely to have good response to ADT

What is the management of biochemical (Mo) HRPC (castrate subset)?

→ rising PSA + no mets (clinical or radiologic) + castrate T

- increasing subset of patients in today's paradigm of PCa

- goal is to prevent clinical mets

- natural hx is not known } some studies show long time to progression (30months) while others show shorter time (9months)

- can use PSA nadir, PSA DT, PSA velocity, Gleason score, initial stage to predict outcomes

Rx → **2nd line hormonal manipulation most commonly employed**

→ PSA trigger point is unknown

→ role of early CEMO unknown

What is the management of metastatic HRPC?

→ rising PSA + mets + castrate T

- goal is to prolong life, reduce pain, and prevent skeletal morbidity

- 90% have bone mets } majority will have + bone scan & PSA progression (70%)

- only 10% have soft tissue/visceral mets } response to Rx in soft tissue sites may not provide significant survival benefit

Rx → **palliative therapy vs systemic CEMO**

→ bisphosphonates

What are the common sites of PCa metastasis?

→ skeletal mets

- axial skeleton (most common)
- sacrum
- L-spine
- ribs
- pelvis

→ non-skeletal mets

- LNs (20%)
- lung (10%)
- liver (5%)
- bladder
- adrenal

What are the causes of anemia in the setting of PCa? } most common hematologic abnormality

- 1) disease-related

- anemia of chronic disease
- BM invasion
- blood loss
- microangiopathic hemolytic anemia associated with DIC

- 2) secondary to treatment

- prior palliative RADs for bone mets
- long term ADT
- systemic CEMO
- systemic radiopharmaceuticals

Rx → Epo +/- Fe supplements

What are the causes of pancytopenia in the setting of PCa?

- 1) systemic CEMO
- 2) extensive RADs
- 3) rapidly growing mets in BM

Which subtypes of PCa develop OSTEOLYTIC mets? } "TSN"

→ **usually get osteoblastic lesions**

- 1) TCC
- 2) Squamous carcinoma
- 3) Neuroendocrine differentiation (small cell)

Which types of tumours develop OSTEOLYTIC bone mets?

- prostatic adenocarcinoma
- Multiple myeloma
- breast Ca (mixed)
- melanoma (mixed)
- stomach
- medulloblastoma
- bronchial carcinoid

EXPERIENCE WITH CYTOTOXIC CHEMOTHERAPY

What are the predictors of response to CHEMO in HRPC?

→ definite

- **performance status**
- **pretreatment Hg levels (10-12 g/dL)**
- presence of pain

→ probable

- post-chemo parameters (eg PSA DT, PSA velocity, etc)
- presence of visceral mets (liver involvement)
- baseline PSA
- time from ADT to initiation of CHEMO

→ equivocal

- extent of bone scan involvement (# of lesions, pattern of distribution)
- continuation of ADT

How does one measure performance status?

→ **ECOG performance status score (Eastern Cooperative Oncology Group)**

- Grade 0 } Fully active, able to carry on all pre-disease performance without restriction
- Grade 1 } **Restricted** in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work)
- Grade 2 } ambulatory & capable of all self-care but **unable to carry out any work activities** up and about more than 50% of waking hours
- Grade 3 } capable of **only limited self-care** confined to bed/chair >50% of waking hrs
- Grade 4 } **Completely disabled** & cannot perform any self-care totally confined to bed or chair
- Grade 5 } **Dead**

Which single agent CHEMO regimes have been used for HRPC?

- 1) docetaxel (Taxotere) } GOOD single agent activity
- 2) paclitaxel (Taxol)
- 3) mitoxantrone } modest subjective benefits (especially for palliation w/ steroids)
- 4) estramustine } some single agent activity (better in combination Rx)
- 5) 5-FU \
- 6) carboplatin } only modest single-agent benefits
- 7) doxorubicin /
- 8) cyclophosphamide } modest anti-tumour effects
- 9) etoposide

What are some of the landmark trials for CHEMO for HRPC?

- 1) Tannock et al, JCO '96 } mitoxantrone + prednisone VS prednisone alone
→ significant improvements in QOL but not survival
- 2) Kantoff et al, JCO '99 } mitoxantrone + hydrocortisone VS hydrocortisone alone
→ significant improvements in QOL but not survival
- **FDA APPROVED MITOXANTRONE + PREDNISONE FOR SYMPTOMATIC METASTATIC PROSTATE CANCER IN 1997**
- 3) Petrylak et al } docetaxel (q3/52) + estramustine VS mitoxantrone (q3/52) + prednisone
NEJM 2004 } → coumadin & ASA added to estramustine arm
(SWOG 9916) } 770 men in RCT
→ overall survival in docetaxel arm 17.5 months vs 15.6 months in mitoxantrone arm (2 MONTH BENEFIT)
→ ~20% relative risk reduction in death BUT estramustine accounted for majority of TOXICITY
- 4) Tannock et al } mitoxantrone (q3/52) VS docetaxel (q3/52) VS docetaxel (q1/52)
NEJM 2004 } concomitant prednisone for all 1006 men in RCT (5mg bid)
(TAX 327) } all patients continued ADT
→ median 20.7 months f/u
→ overall survival in q3/52 docetaxel arm 18.9 months vs 16.4 months in mitoxantrone arm (2.5 MONTH BENEFIT)
→ benefits of qweekly docetaxel not significant
→ ~25% relative risk reduction in death
→ significantly improved pain & QOL scores in docetaxel arms
→ more hematologic toxicity with q3wk docetaxol over q1wk
- **SINGLE AGENT DOCETAXEL q3wks BETTER THAN MITOXANTRONE**
→ **IMPROVES OVERALL & PROGRESSION-FREE SURVIVAL**
→ **IMPROVES PAIN & IMPROVES QOL**
→ **ADDITION OF ESTRAMUSTINE LIKELY OF LITTLE ADDED BENEFIT**

What are the main side effects of DOCETAXOL (taxotere)?

- plant alkylid (anti-MT agent) } induces apoptosis
- **myelosuppression**
- stomatitis
- **redness/soreness of palms & soles**
- loss of finger nails
- peripheral neuropathy
- alopecia
- fluid retention/edema
- N/V, diarrhea, changes in LFTs

What are the main side effects of MITOXANTRONE?

- anthracycline Abx (direct DNA damage)
- **myelosuppression** } dose limiting → few cases of leukemia reported
- **cardiotoxicity (CHF, decreased EF)** } **WORST → MUGA scan for all before Rx**
- hepatotoxicity, nephrotoxicity

What are the main side effects of ESTRAMUSTINE?

- anti-MT agent (cytotoxic) } conjugate of 17 β -estradiol + alkylating agent (nitrogen mustard)
- **5-10% incidence of thromboembolic events** (risk not decreased with ASA or coumadin)
- hypoCa
- GI
- myelodysplastic syndrome

How successful is chemotherapy for HRPC?

- overall survival is 16-18 months } 2-3 month survival advantage
- q3weekly docetaxel + prednisone likely best agent

Neuroendocrine transformation

What are the findings suggestive of PCa with neuroendocrine transformation? (CHART)

- usually are hormone-refractory
- unique expression of receptors similar to other neuroendocrine tumours
 - eg bombesin/gastrin-releasing peptide antagonist, somatostatin, chromogranin A, etc
- usually small cell variant
- 1) frequent visceral mets + rapidly growing soft tissue mets (retroperitoneal disease common)
- 2) relatively low or undetectable PSA
- 3) lytic bone lesions (not the usual osteoblastic pattern)
- 4) brain mets common
- 5) elevated plasma chromogranin levels
- 6) hyperCa (not usually seen)

What are the management options for PCa with neuroendocrine transformation?

- combination CHEMO } cisplatin + etoposide
 - } carboplatin + etoposide
 - } paclitaxel or docetaxel
 - } doxorubicin
- RADs effective for bulky disease, brain mets, critical areas that affect QOL
- combination CHEMO-RADs often necessary for maximal control of disease
- poor overall prognosis

What is the management of hypercalcemia?

- 1) hydration followed by lasix diuresis } stop any thiazides (↑'s Ca reabsorption)
- 2) bisphosphonates } Zoledronic acid (Zometa) 4mg iv q4weeks (not if renal dysfunction)
- 3) steroids
- 4) calcitonin

PALLIATIVE MANAGEMENT OF PATIENTS WITH HRPC

How does malignant cord compression present?

- epidural mets is common } usually from compression by vertebral bodies
- 1) **back pain } present in majority (95%)**
- 2) focal neurological findings } leg weakness, sensory levels
→ once neurologic symptoms present, likelihood of reversal is low
- 3) changes in bladder or bowel function
- 4) autonomic dysfunction

What is the management of metastatic spinal cord compression?

- investigations
 - Hx and P/E
 - imaging } urgent MRI spine (to assess location of lesion)
- management
 - steroids (dexamethasone_ } 10mg iv loading dose followed by 4-24mg iv/po q6h
} improves pain & decreases vasogenic edema
 - spinal RADs
 - surgery + RADs } may have better outcomes in subset
 - systemic radionuclides
 - +/- ketoconazole (400mg po q8h) } fastest non-surgical way to get castrate level of T
} consider bilateral orchiectomy

What are the indications for spine surgery on HRPC patients with cord compression?

- | | |
|---|-------------------------------------|
| 1) evidence of progression during RADs (signs & symptoms) | 5) extensive bone involvement |
| 2) recurrence after RADs | 6) compression caused by bone |
| 3) unstable pathologic fractures | 7) unknown tissue diagnosis |
| 4) high-grade epidural blocks | 8) hx of previous RADs to same area |

What are the changes seen in bone in PCa patients?

- bone loss from enhanced osteoclastic activity associated with long term ADT
- bone mets induce predominantly osteoblastic activity
→ rare to see hyperCa (usually associated with neuroendocrine transformation)

What is the role of bisphosphonates in PCa with bone mets?

- reduces bone resorption by inhibiting osteoclastic activity } ↑s BMD in PCa patients on long-term ADT
- inhibits adhesion of tumour cells to bony matrix
- prevents tumour cell invasion into bony matrix
- inhibit matrix metalloproteinases

What is the role of Zometa in PCa?

- **RCTs with Zoledronic acid (Zometa) have shown a reduction in incidence of skeletal events and an increase in BMD in patients on long-term ADT**
→ Saad et al, JNCI '04 → Smith et al, J Urol '03
- Zometa 4mg iv q3-4 weeks } for progressive HRPC with evidence of bone mets
- other bisphosphonates have not been shown to be beneficial in RCTs

What are the side effects of Zoledronic acid (Zometa)?

- fatigue
- flu-like symptoms } myalgia, fever
- anemia
- hypoCa → should take Ca (1.5g/day) and Vit D (400units/day)
- **severe jaw pain** → rare complication } associated with osteonecrosis of mandibular bone

What are the contraindications to Zoledronic acid?

- 1) hx of poor dentition
- 2) recent or planned dental work
- 3) chronic dental disease
- 4) renal failure

What are the common pain syndromes associated with metastatic HRPc?

- 1) localized bone pain
 - multimodal pain meds
 - localized RADs (lytic mets, weight-bearing areas, extremities)
 - surgical stabilization of pathologic fractures or extensive bone erosions
 - also consider radiopharmaceuticals if RADs fail
- 2) diffuse bone pain
 - multimodal pain meds
 - 'multi-spot' or wide-field RADs
 - radiopharmaceuticals
 - also consider steroids, bisphosphonates, calcitonin, chemo
- 3) plexopathies (caused by direct tumour extension or prior therapy)
 - multimodal pain meds
 - RADs (if no hx of radiation)
 - nerve blocks
 - also consider TCAs, anticonvulsants
- 4) miscellaneous neurogenic pain (eg post-herpetic neuralgia, peripheral neuropathies)
 - multimodal pain meds
 - stop all neurotoxic drugs (eg docetaxel, cisplatin, etc)
 - also consider TCAs, anticonvulsants
- 5) other uncommon pain syndromes (extensive skull mets with CN involvement, or extensive painful liver mets or pelvic masses)
 - RADs
 - multimodal pain meds
 - steroids for CN involvement
 - also consider systemic or intrathecal chemo

What are the different systemic radionuclides used for bone mets?

- ³² Phosphorus } 60-80% response rate w/ ~5month duration but ++ toxicity
- ⁸⁹ Strontium } 60-90% response rate w/ ~6month duration (longest half-life at 50days)
- ¹⁸⁶ Rhenium } 75-80% response rate w/ only 1-2month duration
- ¹⁵³ Samarium } 75-90% response rate w/ only 2-3month duration (shortest half-life at 46hrs)

What is the role of "bone-seeking" radiopharmaceuticals?

- useful for management of "diffuse" bone pain
- strontium 89 } palliation of pain in 25-65%
 - } better if used in combination with RADs
 - } can cause **myelotoxicity (esp if diffuse osteoblastic mets)**
- samarium 153-lexidronam } lower rate of severe myelotoxicity than 89Sr
 - } effective palliation of bone pain

NOVEL APPROACHES

What are the important steps in determining a potential target for novel therapy?

- 1) demonstration of a mutation or functional dysregulation of the target in the diseased state
- 2) showing target is important on its own or in combination with other mutations in reproducing the diseased state
- 3) evidence that inhibition of the target leads to tumour regression or quiescence

What are the important biologic processes under therapeutic investigation in PCa?

- 1) growth and survival pathways
 - candidate pathways include:
 - hedgehog signaling } involved in PCa mets
 - PI3-kinase/Akt signaling
 - MAP kinase signaling
- 2) chemo and hormone resistance
- 3) angiogenesis
- 4) immune surveillance and escape
- 5) stem cell renewal

What are some of the future potential targets for PCa therapy?

- 1) PTEN } loss of tumour suppressor PTEN is found in >50% of PCa mets and correlates with advanced Gleason score, stage, and chemo resistance
 - } PTEN normally inhibits PI3-kinase/Akt pathway
 - activation of PTEN may be potential Rx
- 2) rapamycin } induces apoptosis when given with chemo
 - may induce cell death in patients with Akt activation
- 3) EGF receptor } overexpressed in 40-80% of PCa cells (especially Blacks)
 - EGFR inhibitors may be potential Rx (eg gefitinib)
- 4) PDGF receptor } overexpressed in PCa progression
 - } PI3-kinase/Akt pathway
 - PDGFR inhibitors may be potential Rx (eg imatinib)
- 5) Vit D analogues } anti-proliferation and chemo-sensitizing properties
 - } increased survival when given in combination with docetaxel (+7months)
 - calcitriol may be potential Rx
- 6) Endothelin-1 } likely involved in paracrine signaling between osteoblasts and PCa cells
 - } endothelin A receptors overexpressed in PCa
 - endothelin antagonists may be potential Rx for bone mets (eg Atrasentan)
- 7) Proteasome inhibitors } essential in normal cell cycle regulation and cell death
 - may have role in solid tumours like PCa (eg Bortezomib)
- 8) Dendritic cell-based vaccine } active immunotherapy with vaccination against tumour Ag's
 - CD54+ dendritic cell-based anti-PAP vaccine (Provenge)
- 9) VEGF } elevated levels in PCa progression
 - VEGF antibodies may be potential therapy (eg Bevacizumab, Thalidomide)

ALKYLATING AGENTS

Eg cisplatin, carboplatin, cyclophosphamide, ifosfamide, thiotepa, estramustine, nitrogen mustard

Mode of action: directly damages DNA

Toxicities:

Cisplatin → **nephrotoxicity, ototoxicity, peripheral neuropathy**, Raynaud's, mild cytopenia, N/V, gonadal dysfxn

Carboplatin → nephrotoxicity, ototoxicity, hepatitis, hypoMg, hypoK, peripheral neuropathy, **myelosuppression** (worse than cisplatin)

Cyclophosphamide → cytopenia, **hemorrhagic cystitis, cardiomyopathy**, spermatogenic arrest, SIADH

ANTIMETABOLITES }}} “GM-5”

Eg gemcitabine, MTX, 5-FU

Mode of action: interfere with DNA and RNA division

Toxicities:

Gemcitabine → **nephrotoxic, hepatotoxic**, cytopenia, alopecia

MTX → **myelosuppression**, nephrotoxicity, pulmonary fibrosis (minimized by leukovorin), **stomatitis**

ANTI-TUMOUR ANTIBIOTICS }}} “-mycin's”

Eg bleomycin, doxorubicin/adriamycin, mitoxantrone, mitomycin C, actinomycin-D

Source: from byproducts of fungus Streptomyces

Mode of action: interfere with enzymes involved in DNA replication, preventing RNA synthesis

Toxicities:

Bleomycin → **pulmonary fibrosis**, pneumonitis, Raynaud's (**NO MYELOSUPPRESSION**)

Doxorubicin/adriamycin → cytopenia, **cardiotoxicity**

Mitoxantrone → **cardiotoxicity**, BM suppression, mucositis

MITOTIC INHIBITORS/PLANT ALKALOIDS }}} “VET”

Eg Vinca alkaloids (vinblastine, vincristine), etoposide, taxanes (docetaxel)

Source: plant derivatives

Mode of action: antimicrotubule agents

Toxicities:

Docetaxel → **BM suppression**, redness/soreness of **palms and soles**, peripheral neuropathy, fluid retention

Vinblastine → **neurotoxicity, BM suppression**, glossitis

Vincristine → neurotoxicity, alopecia (**NO MYELOSUPPRESSION**)

Etoposide → mucositis, hepatitis, pneumonia, **BM suppression, secondary malignancies**

General chemotherapy associated toxicities }}} “BASIC”

Toxicity	Comment
1. BM suppression	<ul style="list-style-type: none"> - NOT BLEOMYCIN – therefore does <i>not</i> cause nadir sepsis - leucopenia: granulocytopenic fever (potentially fatal); Tx aggressively - worst agents: <ol style="list-style-type: none"> 1. methotrexate 2. carboplatin 3. vinblastine 4. etoposide (VP-16) - thiotepa is only intravesical therapy which is significantly myelosuppressive; MTC is not
2. Alopecia	-
3. Secondary malignancies	<ul style="list-style-type: none"> - esp. alkylating agents and etoposide - non-lymphocytic leukemia - lymphoma - definite risk 1-4%
4. Infertility	<ul style="list-style-type: none"> - 50% return to N in 24 months after stopping - pre-existing gonadal dysgenesis in remaining testis in some CaT Pts - role of sperm banking
5. Common (nausea, vomiting, etc)	-
MVAC: myelosuppression and mucositis most common S/E	

Chapter #106 – GU Embryology

KIDNEY DEVELOPMENT

What are the 3 subdivisions of the mesoderm?

→ as neural tube develops, mesoderm found on either side of midline differentiates

- 1) paraxial mesoderm (somite)
- 2) intermediate mesoderm
- 3) lateral mesoderm

What are the 3 embryonic sources of the urogenital system?

- 1) intermediate mesoderm
- 2) mesothelium of coelomic cavity (future peritoneum)
- 3) endoderm of the UG sinus

Name the 3 embryonic kidneys?

→ **all 3 develop from the intermediate mesoderm**

1) pronephros } regresses in utero

- present 3rd to 5th week
- non-functioning
- develops as 5-7 paired segments in the region of the future neck and thorax
- develops and regresses in cranial to caudal direction

2) mesonephros } regresses in utero

- develops after the formation of the nephric ducts (Wolffian ducts) at ~4 weeks
- serves as transient excretory organ for embryo until definitive kidney develops
- mesonephric tubules disappear by 4th month } few elements remain into maturity

3) metanephros } becomes permanent kidney

- forms in sacral region starting at 5th wk
- result of ureteric bud (sprouting from distal portion of nephric/Wolffian duct) coming in contact with condensing metanephric mesenchymal blastema
- mesenchymal **blastema-ureteric bud interaction** is key to development of nephrons
→ mesenchymal-epithelial interaction

What are the wolffian duct structures found in males?

- | | |
|---------------------------------|--------------------------|
| - efferent ductules | - ureter |
| - epididymis | - renal pelvis |
| - appendix epididymis (remnant) | - calyces |
| - vas deferens + ampulla | - distal collecting duct |
| - SVs | |
| - ejaculatory ducts | |
| - central zone of prostate | |

What are the wolffian duct remnants found in females?

- epoophoron + paroophoron
- Gartner's duct

What structures develop from the metanephric mesenchyme?

- nephron } glomerulus, PCT, loop of Henle, DCT

What structures develop from the ureteric bud?

- collecting system } collecting ducts, calyces, renal pelvis, ureter

What are the 4 stages of nephron development?

→ **starts with mesenchymal condensation once ureteric bud interacts with blastema**

→ **renal tubulogenesis occurs through mesenchymal-epithelial conversion**

→ more mature nephrons are always located in inner part of kidney, and less differentiated nephrons are found at periphery

stage 1 } renal vesicle

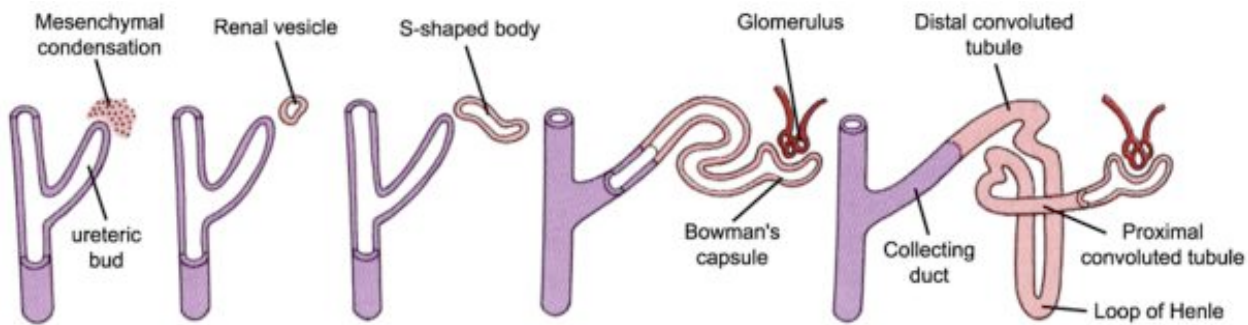
stage 2 } S-shaped body (nephron connects to ureteric bud)

stage 3 } oval-shaped structure

stage 4 } round glomerulus resembling mature renal corpuscle

→ at birth, all nephrons are at varying steps of stage 4

→ **nephrogenesis complete by 34wks**, but maturation continues post-natally



How does the collecting system form?

→ **determined by the dichotomous branching of the ureteric bud**

- 4th week } renal pelvis forms from ampulla of ureteric bud
- 6th week } major calyces form from branches of ureteric bud
- 7th week } minor calyces form from continued branching
- 32nd week } collecting ducts have formed from many generations of bifurcation

What is renal ascent?

- occurs b/w **6th and 9th weeks** } **?differential growth of lumbar & sacral regions** of embryo
- kidney ascends retroperitoneum to rest just below adrenal glands
- as kidneys rise, successive transient aortic sprouts at progressively higher levels supply blood
- final pair of arteries form in upper lumbar region as the definitive main renal arteries (L1-L2)
 - can also see occasional inferior pole arteries } persistent accessory arteries
 - improper ascent results in ectopic kidney, complete failure results in pelvic kidney
- if inferior poles of kidney fuse, horseshoe kidney results } fused LP gets trapped under IMA
- can also get fusion to contralateral kidney during ascent } results in cross-fused ectopy

What transcription factors are important in the development of the nephric duct (Wolffian duct)?

- Pax2
- Sim1
- **Lim1** } essential

What are the 3 cell types essential for renal development?

→ **RET-GDNF-GFR α 1 pathway is important in ureteric bud outgrowth**

1) ureteric bud tip cells

2) condensed mesenchymal cells

3) stromal or interstitial mesenchymal cells

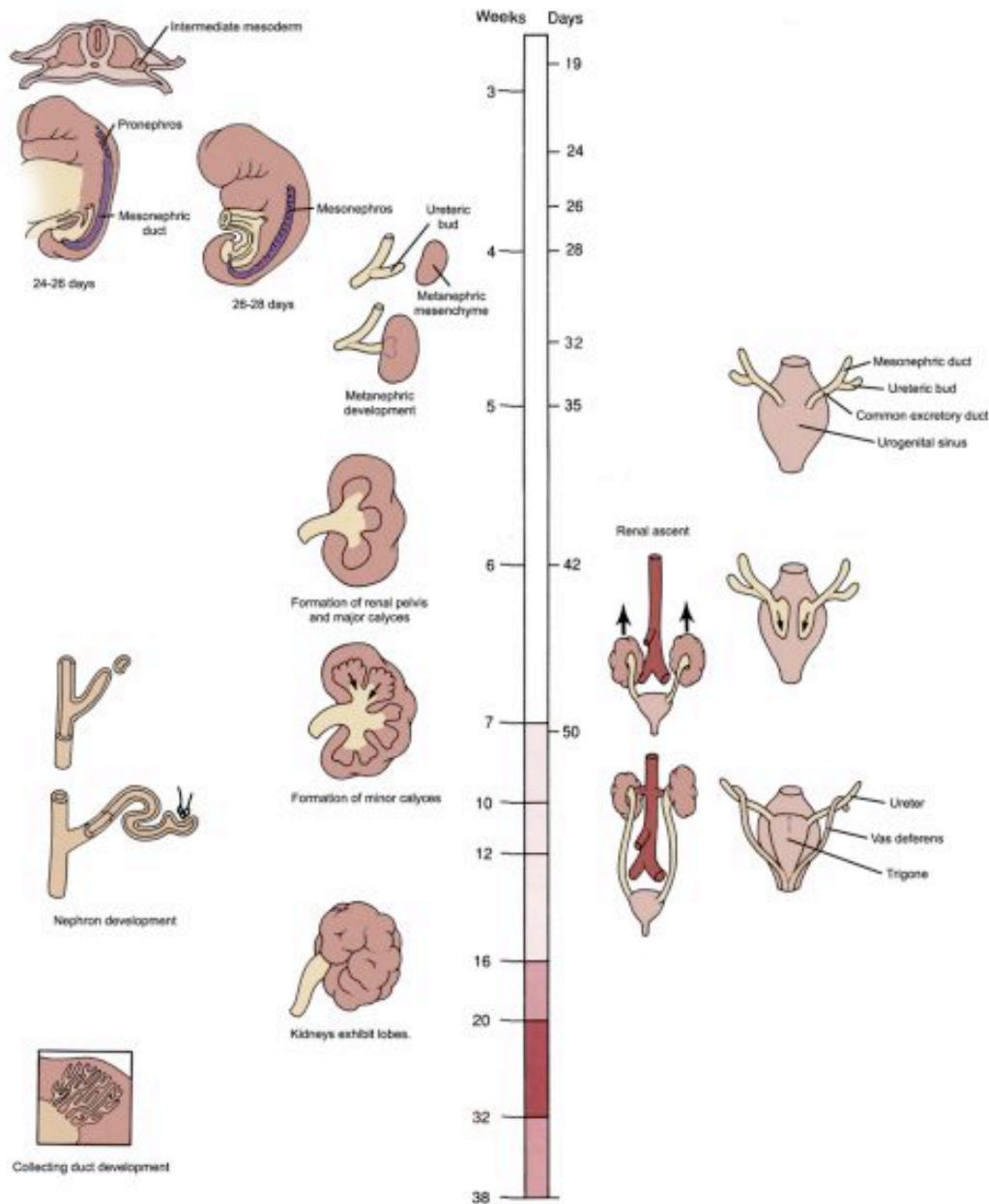
→ inductive signals emanating from ureteric bud promote condensation of metanephric mesenchymal cells around ureteric bud tips and subsequent tubulogenesis

What genes have been proposed to be involved in renal and ureteric development?

- | | | |
|---------------------------|---------|--------|
| - RET-GDNF-GFR α 1 | - Wnt11 | - BF2 |
| - FoxC1/C2 | - Emx2 | - RAR |
| - Pax2 | - Sall1 | - Bmp7 |
| - Eya1 | - Emx2 | |
| - Bmp4 | - Wnt4 | |

What is the origin of the intra-renal vasculature?

- not certain
- both angiogenesis (vessels bud off of aorta) and vasculogenesis (vessels originate in situ from embryonic kidney) likely play a role



A. Kidney development

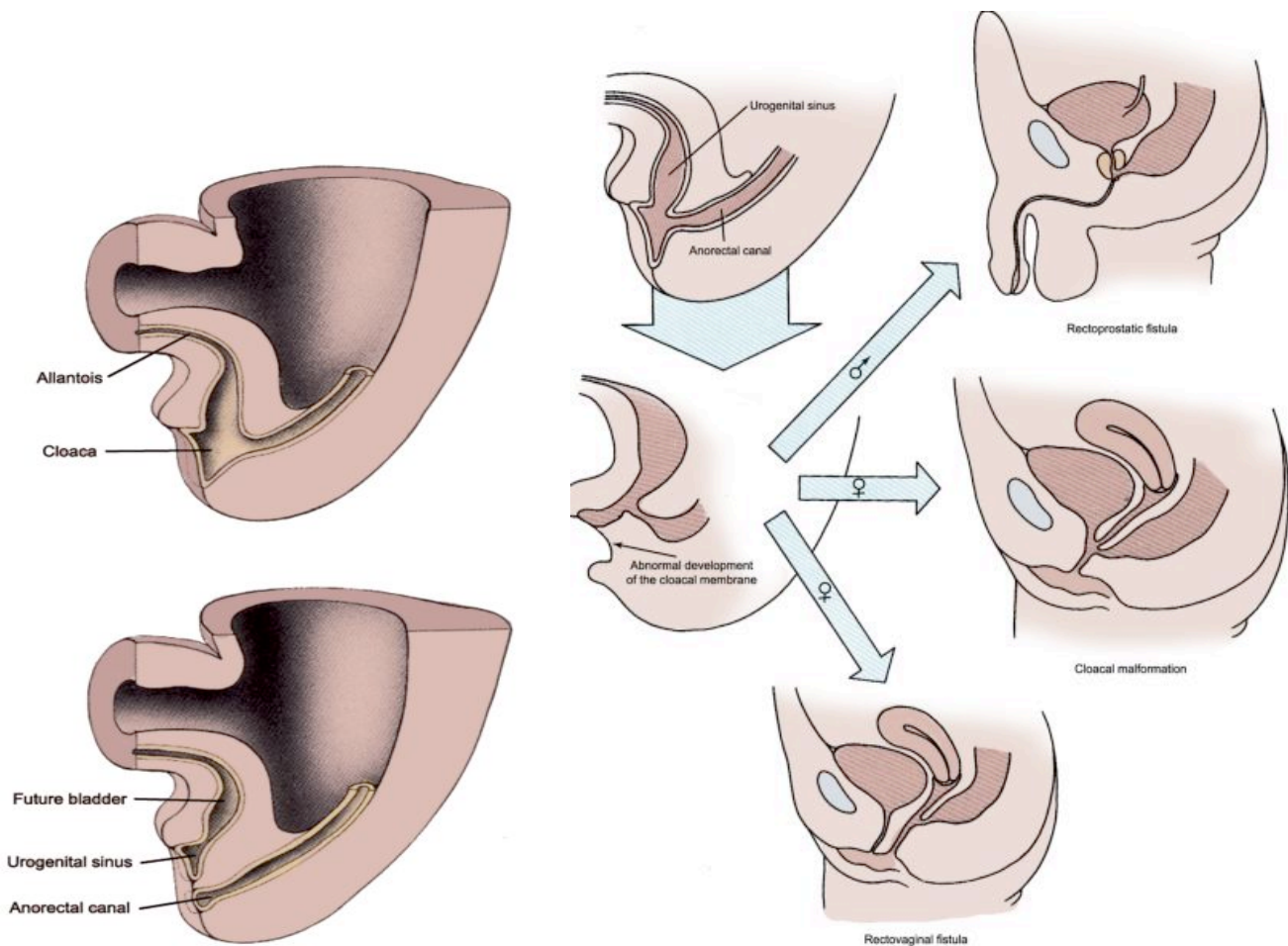
B. Ureter and bladder development

→ URINARY TRACT DEVELOPMENT

BLADDER AND URETERAL DEVELOPMENT

Describe the formation of the cloaca & endodermal UG sinus.

- 4th week } embryo begins to fold so that the cloacal membrane is turned to ventral aspect
 - } terminal portion of yolk sac dilates and becomes the cloaca
- 4-6th week } **wolffian duct fuses with cloaca**, staying with UG sinus during cloacal separation
 - } above insertion of Wolffian duct is the vesicourethral canal (cranial UG sinus)
 - gives rise to bladder and pelvic urethra
 - } below insertion of Wolffian duct is the caudal UG sinus
 - gives rise to phallic urethra (males) or distal vaginal vestibule (females)
- 5th-6th week } **separation of cloaca into anterior UG sinus & posterior anorectal canal** is a result of midline fusion of lateral ridges of cloacal wall + fusion of descending urorectal septum with cloacal membrane
 - new thought is that this doesn't occur at all, and that cloacal membrane development is key to separation of GI and GU
 - } UG sinus is continuous with allantois and its superior portion becomes the bladder



Describe the development of the bladder trigone.

- **common excretory ducts dilate and fuse with the UG sinus to form the primitive trigone**
→ excretory ducts = portion of Wolffian duct distal to ureteric bud outpouching
- **U/O enters bladder by day 37 and migrates in cranial & lateral direction**
→ early entry results in superolateral ectopic position
→ late entry results in inferomedial ectopic position
- Wolffian duct orifice diverges away from U/O and migrates caudally to future site of verumontanum (males) or vaginal canal (females)
→ vas deferens (males) or Gartner's duct (females)

What is the Weigert-Meyer rule?

- in duplex systems, LP ureter tends to be insert more cranial and lateral, while the UP ureter tends to insert more caudal and medial
- abN lateral LP ureter is due to ureteric bud that arises too low on Wolffian duct, resulting in premature incorporation and migration within developing bladder
→ **VUR more likely in LP ureter**
- abN medial UP ureter is due to ureteric bud that arises too high on Wolffian duct, resulting in late incorporation and migration
→ **obstruction more likely in UP ureter**

Where are the most common sites of termination of an ectopic ureter?

→ **the more remote the ureteral opening, the greater the degree of renal maldevelopment**
eg. hypoplasia/dysplasia of an UP segment of a duplicated system

→ males

- **posterior urethra/BN (~50%)**
- SV (33%)
- prostatic utricle (10%)
- ejaculatory duct (5%)
- vas deferens (5%)
- **never distal to EUS so**
NEVER incontinent

→ females

- **urethra (35%)**
- vestibule (34%)
- vagina (25%)
- cervix/uterus (5%)
- urethral tic (<1%)
- Gartner's duct (<1%)
- **can be distal to EUS and so**
CAN BE incontinent

How can the ureter drain into the vas deferens directly?

- ureteric bud arises too high off wolffian duct & doesn't get completely absorbed into developing bladder
→ ureter and vas drain into common duct
- **must be considered if epididymitis + ipsilateral hydronephrosis**

Describe the development of the ureter.

- begins with ureteric bud forming off the wolffian duct (nephric duct)
- acquires complete lumen at 28 days
- **transient luminal obstruction occurs at ~40days** with subsequent recanalization starting in midureter (extends in both directions)
→ Chwalla's membrane (2 cell layers thick) overlying u/o may also be another source of physiologic ureteral obstruction
- ureteral elastic fiber and smooth muscle development occurs at ~12 weeks
- epithelium of ureter starts as simple cuboidal but **changes to transitional at 12-14 wks, with the onset of urine production**

What is the renal-coloboma syndrome?

- rare syndrome of optic nerve (CN2) coloboma + renal anomalies + VUR
- AD inheritance
→ due to mutation of Pax2 gene

What is the BOR syndrome?

- duplex collecting system + renal hypoplasia/dysplasia + renal agenesis
→ due to mutation in Eya1 gene

What is the role of the RAS system in GU development?

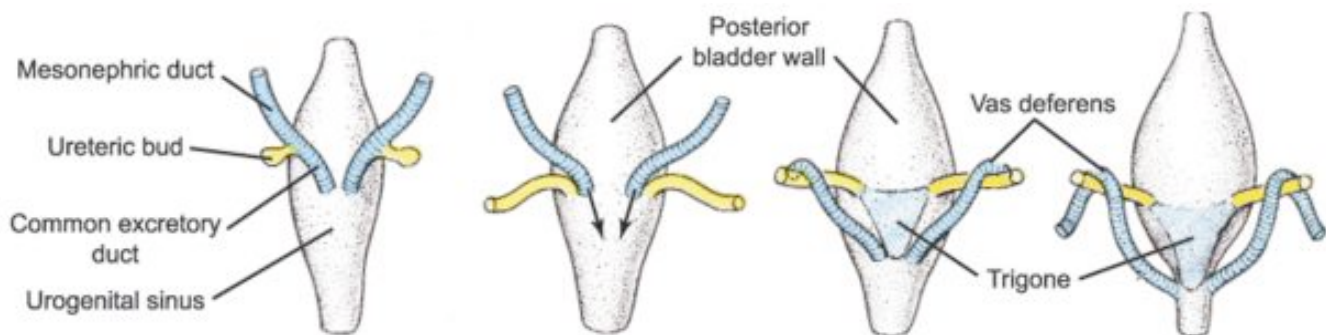
- 1) maintains fetal GFR
 - 2) ensures adequate urine production
 - 3) important for normal growth and development of kidney & ureter
 - fetal ACE inhibition results in anomalies
- AT2 receptors predominate in embryonic structures
 - AT1 receptors predominate in more differentiated structures

What is the embryologic origin of the bladder?

- 1) **bladder body** } **endoderm**-lined vesicourethral canal
 - } portion of **UG sinus** above insertion of wolffian duct
- 2) **trigone** } **mesodermal** structure that develops from the fusion of **common excretory ducts** into the base of the bladder
 - } from **proximal portion of ureteric bud**

Describe the development of the bladder.

- as with other organ development, epithelial-mesenchymal inductive interactions are essential for normal differentiation and development of bladder
- **5th - 6th week** } urorectal septum interacts with cloacal membrane, **separating cloaca into UG sinus anteriorly & anorectal canal posteriorly**
 - UG sinus above insertion of Wolffian duct becomes vesicourethral canal
 - future bladder & pelvic urethra
- **10th week** } bladder is covered by single layer of simple cuboidal epithelium and its apex tapers as urachus, which is continuous with allantois
- **7th-12th week** } smooth muscle of bladder develops, starting at dome
- **12th week** } **urachus involutes** into median umbilical ligament
- **13th-21st week** } urine production starts and urothelium becomes transitional (5 layers thick)
 - see increasing compliance (more smooth muscle, less thick collagen)
- **15th week** } urethral sphincter develops in anterior wall of urethra



GENITAL DEVELOPMENT

Describe the development of the genital ridges and paramesonephric duct.

→ **urinary system development starts before genital system development (3wks later)**

- 5th week } **primordial germ cells** migrate from yolk sac to mesenchyme of posterior body wall ~T10
 - signals existing cells of **mesonephros & adjacent coelomic epithelium** to proliferate & form pair of genital ridges just medial to developing mesonephros
- 6th week } cells of **genital ridge** form supporting cells called **primitive sex cords**
 - } primitive sex cords invest the germ cells and support development
 - develop into **medullary & cortical regions of primitive sex cords**
- 6th week } **paramesonephric (Mullerian) ducts form lateral to nephric (Wolffian) ducts**
 - they arise from invagination of thickened coelomic epithelium
 - } distal Mullerian duct tips are connected as they join UG sinus b/w opening of R & L Wolffian ducts
 - } cranial ends of Mullerian duct open into coelomic cavity (future peritoneum)

What are the early stages of male-female genital differentiation?

→ **sexual differentiation does not occur until 7th week**

1) SRY

- SRY protein induces **medullary primitive sex cords** to become **Sertoli cells**
- without SRY, medullary primitive sex cords degenerate
 - secondary **cortical sex cords** develop and differentiate **into ovarian follicles**

2) MIS

- developing Sertoli cells produce MIS, causing regression of paramesonephric (Mullerian) ducts between 8th-10th week
 - **MIS acts locally and unilaterally**
- male remnants of the Mullerian duct include the appendix testis & prostatic utricle
- without MIS, Mullerian duct structure can form (female internal organs)

3) Testosterone

- **Leydig cells** differentiate from mesenchymal cells of genital ridge in response to SRY protein at 9th to 10th week
- Leydig cells start to produce T between 8th to 12th week
 - T stimulates Wolffian ducts to mature into efferent ductules, epididymis, etc
 - **T is first detectable by 9th week**
 - early T is under control of placental chorionic gonadotropins
 - will eventually be under control of pituitary gonadotropins
- efferent ductules don't establish communication with rete testis until ~3rd month
- presence or absence of T influences development of external genitalia

What is hernia uteri inguinale?

- **genetic M with persistent mullerian duct structures** (uterus & fallopian tubes)
- due to **deficient MIS production** by Sertoli cells or mullerian ducts that **don't respond to MIS**
- may find uterus & fallopian tubes in inguinal hernia

What are the important steps in the development of male genital structures?

- **SRY initiates Sertoli cell development** from primitive sex cords (medullary)
 - if no SRY, then primitive sex cords degenerate and secondary sex cords form ovaries
- differentiating Sertoli cells organize to form testis cords
- at puberty, testis cords that are associated with germ cells become seminiferous tubules
- **Sertoli cells secrete MIS**, which results in degeneration of Mullerian ducts
 - **Mullerian duct remnants in males are the prostatic utricle & appendix testis**
- **SRY also initiates Leydig cell development**, resulting in T production, which stimulates development of Wolffian duct structures
 - forms into efferent ductules, epididymis, appendix epididymis, vas, SVs, ejaculatory duct, etc
- **prostate develops from epithelial cords from UG sinus at 10-12 wks**
 - starts as solid structure and then canalizes
 - however, central zone of prostate is actually a Wolffian structure
 - development depends on circulating fetal androgens & prostate-inducing paracrine signals from UG sinus
- at puberty, prostate size increases rapidly in response to circulating T (Leydig cells)

What are the important steps in the development of female genital structures?

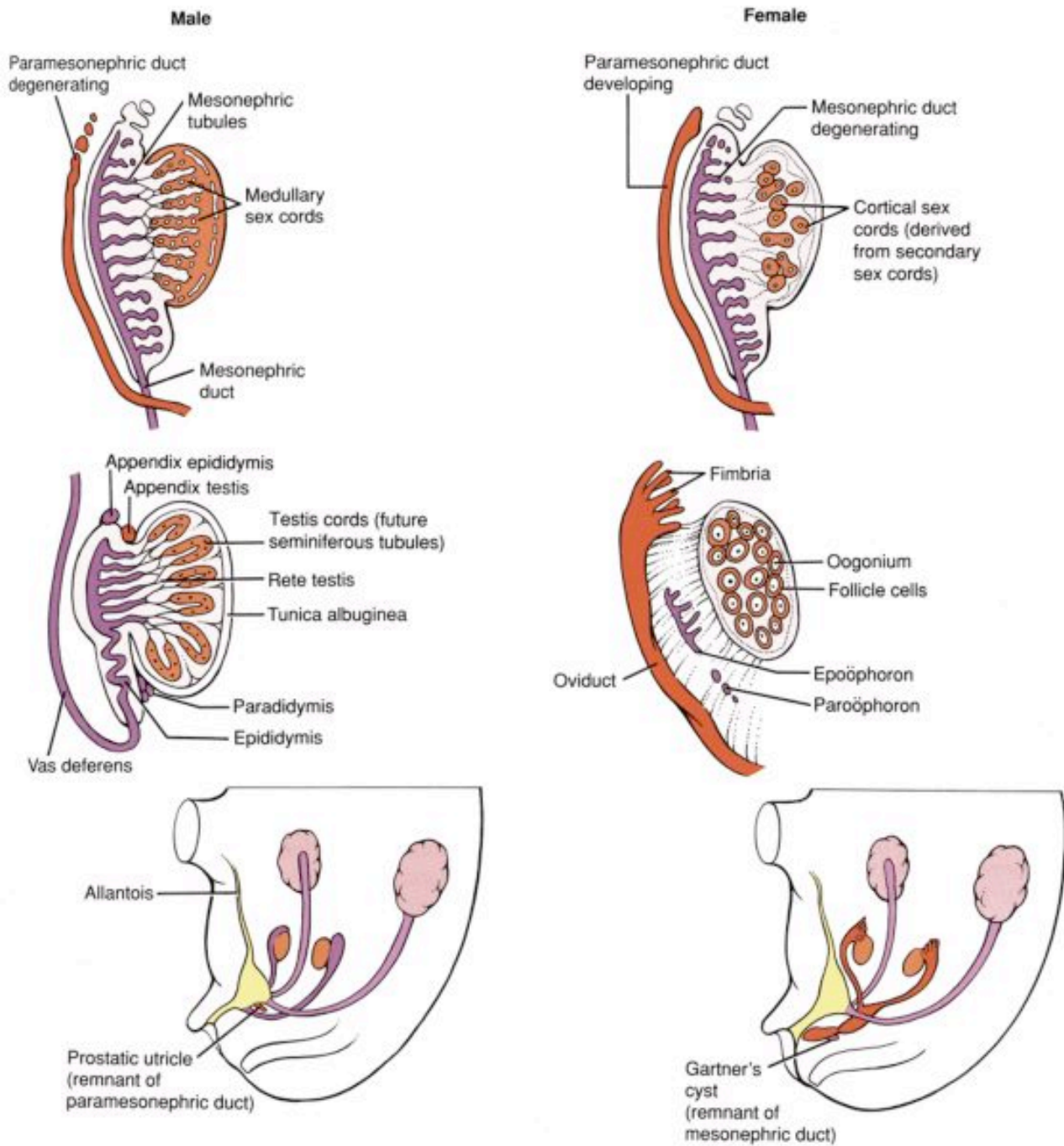
- **no SRY protein**, so **no Sertoli cell & Leydig cell differentiation**
- no Sertoli cell so **no MIS**
- no androgens
- **primitive sex cord degenerate**
- mesothelium of genital ridge forms into **secondary cortical sex cords**, which invest the primordial germ cells to **form the ovarian follicles**
 - germ cells enter first meiotic division as primary oocytes then arrest until puberty
- without MIS and androgens, Wolffian ducts degenerate
 - **Wolffian duct remnants in females are the epoophoron (in mesentery of ovary) and Gartner's duct cysts**
- Mullerian ducts fuse in midline to form the **fallopian tubes, uterus, and upper 2/3 of vagina**
- sinovaginal bulb (posterior aspect of **UG sinus**) develops into vaginal plate, which becomes canalized to form **the lower 1/3 of the vagina**

What are the structures formed by the Wolffian and Mullerian ducts in males & females?

	Wolffian duct structures	Mullerian duct structures
males	<ul style="list-style-type: none"> - efferent ductules - epididymis - appendix epididymis (remnant) - vas deferens + ampulla - SVs - ejaculatory duct - CZ of prostate - paradidymis (remnant) - ureter - renal pelvis & calyces - distal collecting duct 	<ul style="list-style-type: none"> - appendix testis - prostatic utricle - ? verumontanum (colliculus seminalis)
females	<ul style="list-style-type: none"> - Gartner's duct (vas equivalent) - epoophoron, paroophoron (epididymis) - ? appendix vesiculosa 	<ul style="list-style-type: none"> - fallopian tubes - uterus - cervix - upper 2/3 of vagina

What are the structures formed by the UG sinus in males & females?

- | | | | |
|---------|-----------------------------------|-----------|-----------------------------------|
| → males | } bladder | → females | } bladder |
| | } urethra | | } urethra |
| | } prostate | | } Skene's gland |
| | } bulbourethral glands (Cowper's) | | } vestibular glands (Bartholin's) |
| | | | } lower 1/3 of vagina |



→ MALE & FEMALE GONAD AND GENITAL DEVELOPMENT

Describe the early development of the external genitalia?

- **external genitalia are indistinguishable until 7th week**
- **differentiation occurs in response to the presence or absence of T**
 - external genitalia express enzyme 5 α -reductase
 - action of DHT masculinizes external genitalia
- **migration of mesodermal cells (mesenchyme) to midline** results in closure of medial portion of anterior abdo wall, anterior bladder wall, pubic symphysis, & rudiments of external genitalia
 - failure of medial migration of mesodermal cells results in **bladder exstrophy**
- mesenchymal cells migrating to midline spread around cloacal membrane and form swellings
- 5th week } **cloacal folds (swellings)** form on either side of cloacal membrane
 - } cloacal folds meet just anterior to cloacal membrane to form genital tubercle
 - **genital tubercle = glans penis or clitoris**
- cloacal folds flanking opening of UG sinus become urogenital folds
 - urogenital folds become urethral folds
 - **urogenital/urethral folds = penile urethra or labia minora**
- cloacal folds flanking opening of anorectal canal become anal folds
- new pair of swellings appear on either side of urogenital folds, called the labioscrotal folds
 - **labioscrotal folds/genital swellings = scrotum or labia majora**

How does the distal glanular urethra form?

- combination of 2 processes
- 1) fusion of urethral folds proximally
- 2) invagination of ectodermal cells distally (fossa navicularis up to sinus of Guerin)

What are the main steps of gonadal descent?

1) testis

- 7-8th week } prior to differentiation, testis lies near developing kidney (mesonephros)
 - held by 2 ligaments } **cranial suspensory ligament & ventral ligament**
- 10-15th week } testis stays close to future inguinal region during enlargement of abdominal cavity
 - anchored by enlarging **ventral ligament (aka gubernaculum)**
 - androgens result in regression of cranial suspensory ligament
- 3rd month } testis is in pelvis
- 7th month } gubernaculum bulges beyond external ring & descends to **scrotal location** via processus vaginalis
 - processus vaginalis allows testis to exit abdominal cavity
 - bulky portion of gubernaculum resorbs after completion of inguinoscrotal migration

2) ovary

- 7-8th week } prior to differentiation, ovary lies near developing kidney (mesonephros)
 - held by 2 ligaments } cranial suspensory ligament & ventral ligament
- 10-15th week } ovary remains closer to kidney during enlargement of abdominal cavity
 - cranial suspensory ligament persists due to lack of androgens
 - ventral ligament (**gubernaculum**) **involutes to become round ligament**
- 3rd month } ovary is in pelvis
 - gubernaculum does cause some descent of ovary into pelvis

What factors have been theorized to play a role in testicular descent?

- gubernaculum shortening/contraction
- androgens } effects on intra-abdominal ligaments that hold testis
- intra-abdominal pressure } transit through inguinal canal and into scrotum
- MIS
- INSL3 protein } may affect gubernacular growth
 - estrogens suppress INSL3 and is associated with cryptorchidism
- Hoxa-10 protein
- calcitonin gene-related peptide (CGRP) } primary neurotransmitter in genitofemoral nerve

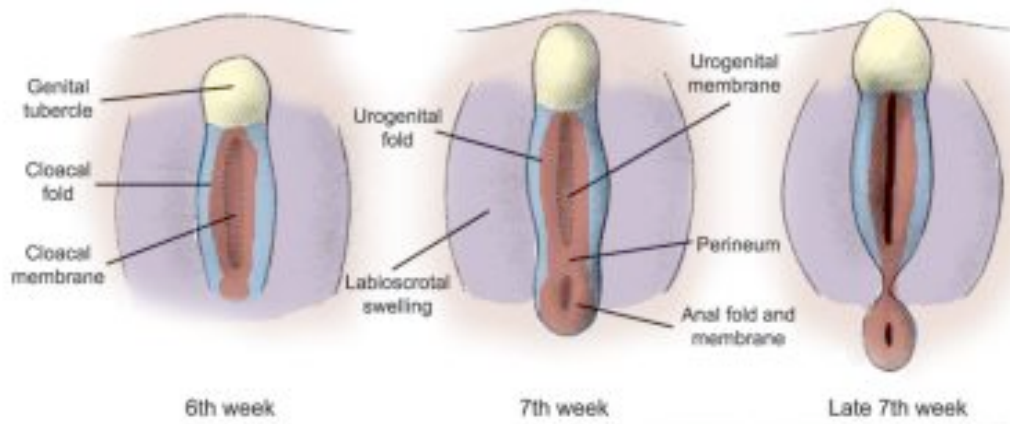
What factors may affect testicular descent?

→ testicular descent is a complex event mediated by both hormonal & mechanical forces

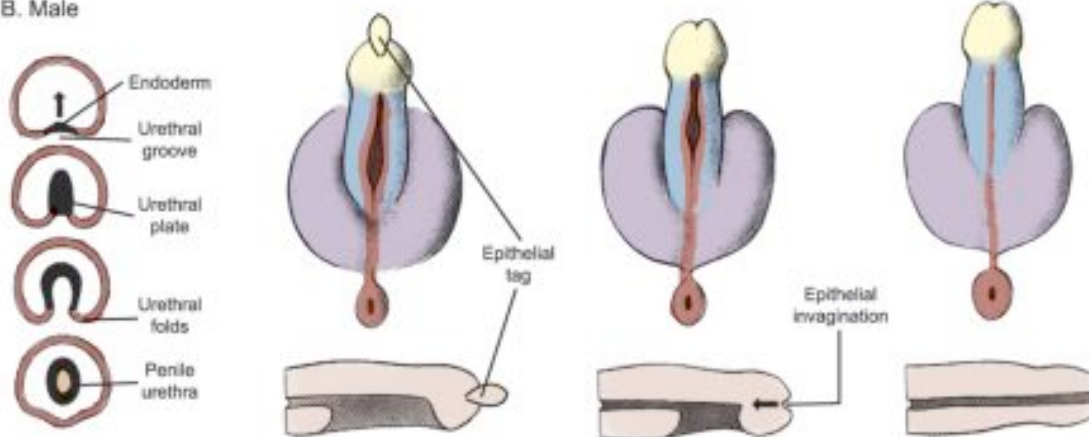
→ “GEGEI”

- 1) Gubernaculum } **major factor responsible for testicular descent**
 - “ventral ligament”
 - possible functions
 - a) guide into the scrotum (no firm attachment) → doesn’t pull testis into scrotum
 - b) wedge that swells and dilates the inguinal path
- 2) **Endocrine**
 - a) Androgens
 - **androgens do not mediate the transabdominal phase of testicular descent**
 - **required for inguinal-scrotal phase of descent**
 - b) MIS
 - MIS secreted by Sertoli cells, responsible for regression of Mullerian ducts
 - levels normally surge in 1st year, peak at 4-12 mo, then decrease w/ age
 - patients w/ cryptorchidism have no surge, levels are decreased
 - **likely has no role in regulation of testicular descent**
 - c) Estrogens
 - prenatal tx w/ DES } associated w/ urogenital abnormalities
 - impairs gubernacular development
 - causes persistence of Mullerian duct structures
 - e) Descendin
 - androgen independent factor → gubernacular specific growth factor
 - believed to be secreted from the testis in androgen-independent fashion
- 3) Genitofemoral nerve (GN) and calcitonin gene-related peptide (CGRP)
 - transection of GF nerve in rats causes UDT } CGRP is a NT in the GF nerve
 - androgens increase the # of GFN cell bodies and promote gubernacular migration
 - androgen blockade (flutamide) inhibits masculinization of GFN & decreases its CGRP content
- 4) Epididymis
 - unknown if epididymal abnormalities are the cause or result of UDT
 - abnormality in epididymis found in 40-90% of UDT
 - epididymis precedes testis into the scrotum
- 5) Intra-abdominal pressure
 - UDT more common in conditions w/ decreased IAP } prune-belly, cloacal exstrophy, omphalocele, gastroschisis
 - more significant role in transinguinal descent
- 6) differential growth of fetus

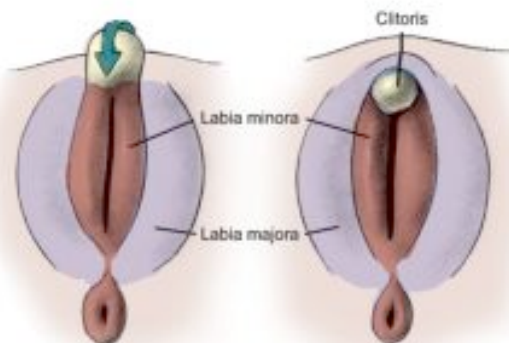
A. Indifferent stage



B. Male



C. Female



Homologues

Male	Female
Prostate gland	Skene's gland
Prostatic urethra	Entire urethra
Prostatic Utricle	Vagina, uterus
Vas, Ejaculatory duct	Gartner's duct
Cowper's glands	Bartholin's glands
Glans	Clitoris
Penile urethra	Labia minora
Scrotum	Labia majora
epididymis	epoophoron, paraoophoron
gubernaculum	Round ligament

Chapter #107 – Pediatric Renal Function

ANATOMIC STAGES OF DEVELOPMENT

Name the 3 embryonic kidneys?

→ **all 3 develop from the intermediate mesoderm**

1) pronephros } regresses in utero

- present 3rd to 5th week } non-functioning

2) mesonephros } regresses in utero

- develops after the formation of the nephric ducts (Wolffian ducts) at ~4 weeks
- serves as transient excretory organ for embryo until definitive kidney develops
- mesonephric tubules disappear by 4th month } few elements remain into maturity
- main role is related to ductal system and formation of ureteric bud

3) metanephros } becomes permanent kidney

- forms in sacral region **starting at 5wks**
- result of interaction b/w **ureteric bud & metanephric mesenchymal blastema**
- most rapid increase in function during mid-gestation (20-30 wks) and development is complete by 35wks (nephrogenesis follows sigmoid curve)
 - most mature nephrons are in inner medulla
 - outer cortical nephrons are last to complete development

FUNCTIONAL DEVELOPMENT IN THE FETUS

When does urine production occur?

- **urine is seen at 10-12 wks } salt & water homeostasis still occurs mainly via placenta**
- **urine production is normally 10-20 mL/kg/hr by birth (~50cc/hr)**

What is the GFR of fetal kidneys?

- RBF correlates w/ gestational age } increases gradually during T2/T3 & sharply at birth
- GFR is theoretically GFR in single nephron x number of functional glomeruli
 - but GFR is much higher in juxtamedullary glomeruli cf subcortical glomeruli
- **GFR parallels renal mass & correlates with gestational age**
 - **neonatal GFR is low } GFR doubles within first 2 wks of life (regardless of age)**

What is the renal concentrating ability of the fetal kidneys?

- **FENa shows negative correlation with gestational age**
 - **fetus produces hypotonic urine with high Na content and in large volumes**
- K excretion increases with gestation } related to rise in fetal aldosterone
- there is maturational increase in glucose transport
- **overall, renal concentrating & acidifying capacity are reduced in first 2 months of life**

EVALUATION OF FETAL RENAL FUNCTION

What is normal fetal RBF?

- 20cc/min at 25 wks
 - >60cc/min at 40 wks
- \ / **low fetal RBF due to increased vascular resistance and decreased # of vascular channels early on**

What is normal fetal urine output?

- 5cc/hr at 20 wks
- 50cc/hr at 40 wks } equivalent of ~1L/hr in adults

What are the normal fetal urinary indices?

- Na is <100 mEq/L
 - Cl is <90 mEq/L
 - osmolality is <210 mOsm/L
 - urine total protein <20 mg/dL
 - β 2-microglobulin <4 mg/L
 - low fetal urine NAG and valine levels
- \ / } normal tubular function
/ } not leaking protein

List antenatal U/S features that are predictive of poor renal functional

- 1) early hydronephrosis (present at <24wks)
- 2) oligohydramnios
- 3) bilateral moderate to severe hydroureteronephrosis (APD \geq 10-15mm)
- 4) evidence of dysplasia (echogenic cortex, microcystic renal changes)
- 5) thick-walled, dilated bladder detected early (in male)

What are the prenatal prognostic variables that predict poor renal function?

- 1) severe oligohydramnios (early is worse)
- 2) early & severe hydronephrosis (present at <24wks with APD \geq 10-15mm)
- 3) renal dysplasia (echogenic kidneys)
- 4) cystic kidneys
- 5) poor fetal urine chemistries
 - Na >100 (inability to retain sodium)
 - Cl >90
 - Osm >210 (inability to retain water and concentrate urine)
 - β 2-microglobulin >10-20 (elevated in renal dysplasia)
- 6) thick-walled, dilated bladder detected early (in male)
- 7) lack of "pop-off" valve (urinary ascites, VURD, bladder tic, urachal fistula, etc)
→ debatable as to whether this is protective

POSTNATAL FUNCTIONAL DEVELOPMENT

What factors predict renal function at birth?

- 1) gestational age at delivery
- 2) intrauterine factors } eg IUGR
- 3) very low birth weight

How much urine does the neonate produce?

- ➔ **all infants should void within first 24hrs of life, regardless of gestational age**
- normal is ~50 cc/hr
 - oliguria = <1cc/kg/hr
 - polyuria = >2L/1.73 m²/day

What is the normal GFR in a neonate?

- renal blood flow increases gradually during 2nd half of pregnancy
- GFR is theoretically GFR in single nephron x number of functional glomeruli
→ but GFR is much higher in juxtamedullary glomeruli cf subcortical glomeruli
- **GFR parallels renal mass & correlates with gestational age**
→ neonatal GFR is low } GFR doubles within first 2 wks of life (regardless of age)
- **in premies <34wks, GFR at birth is normally below 10 mL/min/1.73 m²**
- **GFR reaches adult levels by age 2**
- GFR in very low birth weight infants DOES NOT catch up to age-matched infants of same post-conceptual age until after 9 months of age

What are causes of the rapid increase in GFR during the first 2 weeks of life?

- 1) diminished renal vascular resistance
- 2) increasing perfusion pressure
- 3) increasing glomerular permeability
- 4) **increasing filtration surface**

What is the tubular concentrating ability of the neonatal kidney?

- tubular function changes inversely with the rise in GFR
→ FENa is below 1% in term infants
- however, there is a **blunted response to Na loading due to the lack of increase in FENa**
- conversely premies <35wks, subject to Na deprivation, may develop hyponatremia due to tubular immaturity and Na wasting
→ **hyponatremia common in premies } may need Na supplementation**
- **neonate can dilute urine fairly well (25-35 mOsm/L) but has limited concentrating capacity (600 – 700 mOsm/L)**
→ worse in premies (500mOsm/L)
→ improves w/ age } by 2 months of age, infant can concentrate urine >1000 mOsm/kg

Why do neonatal kidneys have limited concentrating ability?

- 1) anatomically immature renal medulla
- 2) decreased medullary concentration of NaCl and urea
- 3) diminished responsiveness of collecting ducts to ADH

How does the neonatal kidney respond to acid/base disturbances?

- **reduced threshold for HCO₃ reabsorption**
→ gradually increases with age and increasing GFR
- **inability to respond to acid load**
→ premies are often slightly acidotic } improves by 4-6 wks postnatally

How does Ca/PO₄ metabolism change after birth?

- PTH is suppressed at birth } serum Ca falls, causing increase in PTH
- tubular reabsorption of PO₄ is high if premature } remains high until regular feeding starts

EVALUATION OF RENAL FUNCTION IN THE INFANT AND CHILD

Why is it hard to measure GFR in an infant?

- 1) hard to get accurate 24hr urine collection without catheterization
- 2) measurement of serum Cr not precise at low levels } nadirs by ~7 days (term or near-term babies)
- 3) neonatal kidney has enhanced tubular reabsorption of creatinine
- 4) GFR changes very rapidly w/ N growth } **creatinine in term baby is usually <40**
 } creatinine in premie may be as high as 90 for 1st month

How do you measure GFR?

- can't be measured directly }
 - 1) renal clearance
 - 2) plasma markers
 - 3) formulae

How do you calculate CrCl in infants?

→ CrCl rapidly increases during first 2 yrs } after 2yrs CrCl is fairly constant at 80-140 mL/min/1.73m²
→ should correct for adult surface area

- 1) Schwartz formula
 - $\text{CrCl} = \frac{k \times L}{\text{serum creatinine}}$ → $k = 0.33$ for preterm, 0.45 for full-term, 0.55 for kids
→ $L = \text{body length (cm)}$
- 2) based on 24hr urine collection
 - $\text{CrCl} = \frac{\text{Urine Cr} \times \text{urine volume}}{\text{serum creatinine}}$
- 3) DTPA renal scan
 - precise measurement of GFR + differential function
 - tracer is cleared only by glomerular filtration

What is the predictive value of GFR in infants with renal dysplasia?

- **estimated GFR at 6months $<15 \text{ mL/min/1.73m}^2$** is predictive of early renal failure

How can Na excretion be measured in the neonate?

- 1) 24hr urine Na excretion
 - **Na balance is negative immediately after birth**
 - then as neonate, kidney keeps Na } **hyperNa state needed for somatic growth**
 - in older kids, urinary Na excretion is generally equivalent to Na intake
 - **normally 1-3 mEq/kg/day (reflects amount of Na ingested over last day)**
- 2) FENa
 - can help discern pre-renal from renal/post-renal causes of oliguria
 - isolate tubular from glomerular contribution of Na excretion
 - $$\text{FENa} = \frac{[\text{urinary Na} \times \text{serum creatinine}]}{[\text{serum Na} \times \text{urinary creatinine}]} \times 100\%$$
 - infant FENa <1% suggests pre-renal condition \ neonate can't concentrate
 - neonatal FENa <2.5% suggests pre-renal condition / urine very well

What are the causes of increased FENa?

- renal Na wasting
- adrenal insufficiency
- SIADH

When should one suspect RTA in an infant?

→ consider any child with FTT } chronic acidosis causes growth impairment

- 1) nephrocalcinosis
- 2) stones
- 3) presence of non-AG metabolic acidosis (N gap = 5-15 mEq/L)

What are the indications for evaluation for RTA? → “ACID Paint BRUSH”

- Azotemia
- CaPO₄ stones
- Infants & kids with FTT
- Decreased K
- Pyelo (chronic)
- Bilateral stones
- Recurrent stone formers (>2/yr)
- Unexplained metabolic acidosis (NAG)
- Sponge kidney } MSK, medullary nephrocalcinosis
- Hypocitraturia

How can one classify RTA?

- type 1 } distal RTA (“classic”)
 - defective distal tubular (collecting duct) H secretion
 - **high urine pH (>5.5)** despite low serum HCO₃
 - see Ca PO₄ stones
 - type 2 } proximal RTA
 - decreased threshold for proximal tubular HCO₃ reabsorption
 - **low urine pH (<5.5)** with mildly low serum HCO₃
 - more common in **kids** & often associated with **Fanconi’s**
 - **no stones**
 - type 4 } impaired H and K secretion in distal tubule
 - associated with renal failure, HTN
 - due to aldosterone deficiency or resistance
 - **low urine pH (<5.5) + hyperK**
- NB during first 3 wks of life, threshold for HCO₃ reabsorption can be as low as 14.5 mEq/L in the N infant and SHOULD NOT be regarded as RTA
- congenital hydronephrosis can also result in type 1 or type 4 RTA in infant or child (acquired RTA)

What are the sequelae of RTA in kids?

- growth retardation
- osteodystrophy
- nephrocalcinosis
- stones
- polyuria

How do you test for RTA?

- 1) **serum lytes (low bicarb, hypoK)**
- 2) **venous blood gas (non-AG metabolic acidosis)**
- 3) **urine pH**
 - if AG metabolic acidosis consider ARF or ingestion of organic acids
 - if non-AG metabolic acidosis, ensure no diarrhea
 - acidosis + high urine pH = type 1
 - acidosis + low urine pH +/- hypoK = type 2
 - acidosis + hyperK + low urine pH = type 4

What investigations are needed in the work-up of RTA?

- **most common cause of RTA in kids is congenital obstructive nephropathy & Fanconi’s**
- serum lytes, Ca, PO₄, PTH, thyroid function
 - urinalysis to r/o glucosuria
 - 24hr urine for CrCl, protein excretion, and Ca excretion
 - U/S abdo to look for hydronephrosis, nephrocalcinosis, stones

What is the treatment of RTA in kids?

- type 1 } NaHCO_3 or K citrate
→ 3 mEq/kg/day divided qid
- type 2 } NaHCO_3 and K supplementation
→ 3 mEq/kg/day divided qid
- type 4 } mainly directed at controlling hyperK
→ lasix, HCTZ, kayexalate
- } treatment of acidosis
 → NaHCO_3
- } treat aldosterone deficiency
 → fludrocortisone

What are the causes of poor urinary concentration in infants?

- **consider screening if excessive urine output, unexplained dehydration or hyperNa**
- **renal maldevelopment (dysplasia and obstructive nephropathy)**
- **interstitial nephritis (pyelo)**
- **renal failure**
- RTA
- sickle cell nephropathy
- medullary cystic disease

What lab test will r/o an abN'ity of urine concentration?

- urine specific gravity } if >1.020 , no serious abN'ity
- diabetes insipidus usually <1.005 } needs formal water deprivation test in hospital
 - 1) fluid restriction in morning with close monitoring of wt and vitals
 - 2) perform until 3% loss of body wt, urine osmolality $>600\text{--}800\text{ mOsm/L}$, or tachycardia/hypoTN
 - 3) if fail to produce concentrated urine despite this, give DDAVP intranasally on 2nd day
 - 4) send to endocrine if +ve renal response (ie central DI)

What is the most common cause of hypercalciuria in neonates?

- administration of calciuric drugs } lasix, glucocorticoids (pulmonary dysplasia)
- at risk of stone formation

How is urinary Ca excretion determined in a neonate?

- urinary Ca/Cr ratio (random sample)
- normally <0.2 in older child, <0.4 in infant on breast milk, and <0.8 in preterm infant
- **elevated urinary Ca/Cr ratio predicts future stone formation**

What is the N serum PO_4 in kids?

- should be $>4\text{mg/dL}$
- if <4 , look for renal phosphorus wasting } proximal tubular disorder → need to r/o hyperPTHism

What is the test used to assess for renal PO_4 wasting in kids?

- **reabsorption of PO_4 is high early on in life**
- fractional tubular reabsorption of phosphorous (TRP)
$$\text{TRP} = 100\% \times [1 - (\text{UPO}_4 \times \text{PCr}) / (\text{PPO}_4 \times \text{UCr})]$$
- N is $>95\%$ in term infants, $>75\%$ in premies
- N is $>85\%$ after neonatal period

What is the most common cause for glucosuria in hospitalized infants?

- iv glucose given at rates $>$ tubular reabsorptive threshold

How well does the kidney handle glucose and amino acids?

- ability of proximal tubule to reabsorb glucose is low in premies cf term babies and older kids
→ some glucosuria is normal in early neonatal period
- proximal tubule of neonate is also limited in its ability to reabsorb amino acids cf older kids
→ some aminoaciduria is normal in early neonatal period

What are the complications of overhydration & dehydration in an infant?

→ overhydration

- opening symptomatic patent DA
- cerebral intraventricular hemorrhage
- necrotizing enterocolitis

→ dehydration

- hypoglycemia
- hyperbilirubinemia
- hyperosmolality

What are the normal fluid requirements of a neonate?

- start at 50-80 ml/100kcal of formula } to replace urinary losses
- insensible water loss depends on weight, environment (eg incubator vs radiant warmer), etc
- Na 2-3 mEq/kg/day (once starts to urinate)
- KCl 2 mEq/kg/day (once starts to urinate)

What is the typical renal functional status of a neonate?

→ **gestational age at birth is most important determinant**

- neonatal GFR is low
 - GFR doubles within first 2 wks of life (regardless of gestational age)
 - GFR in premies <34wks is usually <10 mL/min/1.73m² at birth
 - GFR reaches adult levels by age 2
- reduced renal concentrating ability in first 2 months
 - stays reduced longer in premies
- reduced renal acidifying capacity in first 2 months
 - reduced threshold for HCO₃ reabsorption
 - premies are slightly acidotic
- all infants should void within first 24hrs (regardless of gestational age)
 - oliguria is <1cc/kg/hr and polyuria is >2000cc/1.73m²/day
- Na balance is negative immediately after birth but then as neonate, kidney keeps Na
 - hypoNa common in premies
 - hyperNa state needed for growth
- reabsorption of PO₄ is high early on in life
- mild glucosuria & aminoaciduria in premies

HORMONAL CONTROL OF RENAL FUNCTION DURING DEVELOPMENT

What is the impact of RAS on fetal and neonatal renal function?

- renal development in the fetus is related to RAS } fetus has high renin content
 - **maternal ACEi can result in neonatal renal insufficiency**
- in neonate, renin is localized to JG apparatus } similar to adults
 - there is an 8-fold decrease in renal renin mRNA
 - may be due to increased sensitivity to AT II
- PRA is low during fetal life but markedly increases early after birth
 - triggered by vaginal delivery
- adrenal response to AT increases during late fetal & early neonatal period
 - able to maintain hemodynamics better in late fetal and early neonatal period
- late fetal and neonatal GFR is highly dependent on AT-mediated efferent arteriolar tone
 - fetal and neonatal GFR is very sensitive to exposure to ACE inhibitors

What are the effects of ANP?

→ ANP is secreted by cardiac myocytes

- increases GFR
- increases natriuresis
- increases diuresis
- inhibits renin & aldosterone release
- vasorelaxation
- increases vascular permeability

What is the role of ANP in fetal and neonatal renal function?

- serum **ANP levels are high in first several days of life, then decreases** with maturation
→ plays a role in physiologic postnatal natriuresis and diuresis
- but ANP doesn't cause as much natriuresis and diuresis as in adults
→ **neonate needs slightly high Na environment for rapid somatic growth**

What is the role of vasopressin (ADH) in fetal and neonatal renal function?

- fetus has higher levels of ADH in circulation
- BUT fetal **collecting ducts are less sensitive to ADH** compared to adults
- ADH responsiveness develops fully in neonatal period

What is the role of PGs in fetal and neonatal renal function?

- maternal PGs progressively increase during pregnancy } crosses placenta
- PG levels are high in fetus and neonate } important in renal development
→ maternal NSAIDs can result in renal insufficiency & oliguria in neonate
→ NSAIDs result in inhibition of PGs, resulting in increased renal vasoconstriction
- neonatal NSAIDs (eg indomethacin for patent ductus arteriosus) can also result in ↓'d GFR & oliguria

What is the impact of nitric oxide on fetal and neonatal renal function?

- NO is a potent endothelium-derived relaxing factor
- important in maintaining RBF and to counteract other renal vasoconstrictive agents

THE FUNCTIONAL RESPONSE OF THE DEVELOPING KIDNEYS TO MALFORMATION OR INJURY

What are the causes of impaired renal function in the neonate (CHART)?

- 1) congenital anomalies of the kidneys and GU tract
- 2) perinatal vascular accident } renal embolus or renal vein thrombosis
- 3) circulatory disorders } asphyxia, septicemia, etc
- 4) iatrogenic/toxic nephropathy

What is compensatory renal growth?

- compensatory growth of N kidney in response to contralateral, non-functioning kidney
- occurs even in fetus
→ increased excretory burden is not necessary (placenta is filter for fetus)
→ likely related to alterations in growth factors or inhibitors
- **compensatory growth in neonate greatly exceeds that in adult**
→ **mostly hypertrophy, but also some hyperplasia**
- **functional adaptation (GFR) by remaining nephrons also greater in neonates than adults**
- compensatory renal growth due to partially fxn'ing contralateral kidney is much more gradual
→ by the time compensatory renal growth is detected, there is significant progression of renal dysfunction in contralateral kidney

What is the impact of congenital GU tract obstruction on renal development?

- **timing of obstruction is most important wrt renal development**
- complete ureteral obstruction during early gestation results in dysplastic kidneys
→ eg ureteral atresia leads to irreversible MCDK
- complete ureteral obstruction LATER in gestation does not result in dysplastic kidneys
→ eg UPJO (occurs later) leads to impaired renal function, but not MCDK
- early decompression can minimize impairment of renal function
- even in early postnatal period, **maturing kidney more susceptible to injury than adult kidney**
→ may be due to ↑'d renal vascular resistance of immature kidney & the ↑'d activity of RAS

What is the role of renal scans after surgical relief of GU tract obstruction in the neonate?

- may be misleading } can falsely look better
 - functional adaptation by a group of nephrons may mask deterioration of others
- long-term follow-up studies are essential

What is the impact of circulatory disturbances on renal development?

- **young kidney autoregulates RBF at lower perfusion pressures than adults**
- early reduction in renal mass results in impaired autoregulation
 - solitary functioning neonatal kidney may be at greater risk for renal ischemia in presence of hypoTN, etc
- **perinatal circulatory disorders can result in many persistent glomerular & tubular functional abnormalities**

What is the impact of nephrotoxic agents to renal development?

- **developing kidney seems to be more resistant than adult to some nephrotoxic agents**
 - eg aminoglycosides, cisplatin
- fetal exposure to NSAIDs or ACE inhibitors can significantly impair N renal development

How well does the developing kidney recover from renal injury?

- early renal injury delays maturation of renal microvasculature, glomeruli, tubules, & interstitium
 - can lead to permanent renal impairment

What is the prognosis of congenital vs acquired renal disease?

- glomerular hyperfiltration & glomerular hypertrophy have been implicated in progression of most forms of renal insufficiency
- there's a **greater response by remaining nephrons in neonates**
 - theoretically, there's a greater risk than the adult for long term renal dysfunction
- **↓'d renal mass in immature kidney results in greater proteinuria & glomerular sclerosis**
 - than in the adult kidney
 - we don't know what is the critical number of functioning nephrons, below which renal dysfunction is inevitable
 - >25% of kids undergoing Nx develop renal insufficiency & proteinuria as adults

Chapter #108 – Congenital Urinary Obstruction

INTRODUCTION

How common is obstructive uropathy?

- **most common cause of renal insufficiency in boys <1yr of age**
- **most common cause of ESRD requiring renal Tx (~25%)**

How does obstruction usually present in kids?

- **most cases are now detected on prenatal U/S**
- those with clinical manifestations are often severe obstructive conditions } eg PUVs
 - occasionally, clinical signs of obstruction are present } UTIs, pain, HTN
 - decreased GFR (rise in serum creatinine) = glomerular injury
 - acidosis = tubular injury
 - nephrogenic DI = collecting duct abN'ity
- those with lesser degrees of obstruction have a more variable spectrum of altered function

What are the 2 main forms of progressive renal dysfunction?

- 1) uncorrected, partially obstructive lesion
 - eg UPJO
 - initially intact renal function that progressively deteriorates
 - challenge is predicting which lesions will cause progressive renal dysfxn } most do
- 2) previously obstructed, but corrected lesion that has caused some degree of renal damage
 - eg PUVs
 - damaged kidney doesn't have functional reserve to maintain function over time
 - kidneys demonstrate steady decline in function over time
 - could be related to hyperfiltration of remaining renal units
 - challenge is to determine whether early intervention would protect future renal fxn

What are the best predictors of future progressive renal dysfunction?

- few predictors available
- 1) altered absolute renal function } CrCl or serum creatinine
 - relatively insensitive in early stages of progression
- 2) renal scans may be helpful

What is the predictive value of GFR in infants with renal dysplasia?

- **estimated GFR at 6months <15 mL/min/1.73m²** is predictive of early renal failure

What is the difference b/w congenital obstructive uropathy and acquired obstruction in a mature kidney?

- congenital obstruction } lesion that leads to deterioration of renal function AND impairment of renal functional development
 - obstruction develops simultaneously w/ formation of kidney
- acquired } lesion that leads to deterioration of renal function

PATTERNS OF CONGENITAL OBSTRUCTIVE NEPHROPATHY

What is the etiology of renal dysplasia?

- unknown
- often associated with congenital severe obstruction
 - dysplasia often absent with lesser degrees of obstruction
- may also be unrelated to obstruction and due to very early abnormalities in renal development
 - renal induction problem

What changes are seen in the developing kidney secondary to congenital obstruction?

- depends on time and severity of obstruction
- there seems to be a threshold effect of the obstructive effects on renal growth regulation
- 1) distorted regulation of growth
 - hypoplasia, not just atrophy
 - adults only show atrophy
- 2) alterations in tissue differentiation
 - loss of corticomedullary differentiation
 - delayed maturation of renal cell types } glomerulus, tubule, collecting duct
 - } interstitial cells, microvasculature
 - dysplasia
 - alteration in differentiation of cells NOT seen in adults
- 3) alterations in structure
 - **dysplasia**
 - **fibrosis**
 - increased interstitial tissue
 - abN glomeruli
 - abN tubules
 - alteration in amount of renal tissue elements

PATTERNS OF EFFECT

What are the 4 main effects of obstruction on the developing kidney?

- 1) alterations in regulation of growth (hypoplasia)
- 2) alterations in tissue differentiation (dysplasia)
- 3) alterations in structure (ECM and fibrosis)
- 4) alterations in functional integration of kidney (result of the above)

GROWTH

What are the main alterations in growth that occur secondary to congenital obstruction?

- small kidney in infant is not due to atrophy, as in adult } represents **hypoplasia**
- results in reduced # of nephrons & smaller sized nephrons
- differential growth impairment within nephron segments may also be present
- initially may have N renal function but after prolonged recovery, function of the remaining nephrons deteriorate } hyperfiltration injury

What is the significance of growth acceleration secondary to congenital obstruction?

- may see increased renal mass in association with obstruction
 - usually partial
 - timing of obstruction is hard to ascertain
- may occasionally see hyperfunction
- may lead to glomerular sclerosis as seen in early DM
 - growth acceleration followed by glomerular sclerosis

How does congenital obstruction effect growth regulation?

- **obstruction has been shown to alter expression of growth regulatory genes**
 - eg EGF, IGF-I, catalase, HGF
- **obstruction increases apoptotic activity via enhancement of apoptosis-regulating molecules**
 - eg TGF- β 1, p53, FAS, caspases, and BAD

DIFFERENTIATION

What are the effects of congenital obstruction on renal tissue differentiation?

- **dysplasia** results with severe disruptions of renal tissue differentiation
- may be due to obstruction but also can't r/o abN renal induction as a cause
 - ureteric bud-metanephric mesenchyme interaction
- **alteration in differentiation of cells does not occur in adult obstruction to any significant degree**
- disruption of differentiation can occur early or late in renal development
- some are reversible, but most alterations are irreversible
- **obstruction must be severe & early in development to consistently produce dysplasia**

What is the hallmark histologic sign of renal dysplasia?

- **presence of fibromuscular collars around tubular structures (primitive ducts)**
- presence of collagen in kidney = dysplasia
- stains +ve for α -SMA (smooth muscle actin)

FIBROSIS

What are the effects of congenital obstruction on renal tissue structure?

- **fibrosis is a universal characteristic of obstructive nephropathy } although non-specific**
- infiltration of interstitium with **abN amounts of ECM** } collagens, fibronectins, etc
 - ECM in normal amounts is essential to a normally functioning kidney
- cell regulation & cell-to-cell signaling is disrupted
- tissue oxygenation also impaired

Why does congenital obstruction cause increased renal ECM (fibrosis)?

- 1) increased synthesis of collagen
 - upregulation of collagen gene expression } TGF- β , PDGF, renin-AT system (RAS)
- 2) abN TIMP and MMP activity
 - ECM breakdown is controlled by MMPs (degraders) & TIMPs (inhibitors of MMP)
- 3) decreased NO production
 - NO reduces degree of interstitial fibrosis

FUNCTIONAL INTEGRATION

What is the role of inflammation in congenital obstruction?

- **inflammation often found in acquired obstruction**
- **inflammation is absent in congenital obstruction**
- inflammation may begin to play a greater role in congenital obstruction with increasing age
 - seems to be more related to presence of infection
 - **angiotensin is key modulator of many inflammatory responses to obstruction**

What is the role of RAS in congenital obstruction?

- expression of renal renin is increased in obstructed kidney but decreased in contralateral one
- also get increased recruitment of renin-secreting renal cortical cells in obstructed kidney
 - increased renin production resembles early fetal kidney
 - persistence of immature renal vascular regulation (may be neurally-related)
- increased levels of AT1 receptor } mediates vasoconstriction & growth alterations
- decreased levels of AT2 receptor } mediates vasodilation & renal growth

What is the impact of congenital obstruction on tubular function?

- tubules responsible for acid-base homeostasis, electrolyte balance, urinary concentration, and Vitamin D homeostasis
- obstruction can lead to abN tubular function in the affected kidney
- contralateral N kidney compensates for abN tubular function in obstructed kidney so clinical impact is not significant
- **tubuloglomerular feedback, the mechanism for regulating the amount of fluid delivered to the tubules by the glomerulus, is significantly altered in obstructed kidney**

REVERSAL OF CONGENITAL RENAL OBSTRUCTION

Is congenital obstruction in the fetus reversible?

- **functional salvageability of a unilaterally obstructed kidney is dependent on duration of obstruction and gestational age**
- severity of obstruction is also important
- complete reversal of damage is seldom seen
- only crude measures of salvageability exist
 - urine Na, urine Cl, urine osmolarity, urine Ca, urine β 2-microglobulin
- **when fetal urine approaches serum, irreversible damage is likely**

What are the normal FETAL urinary indices?

- Na is <100 mEq/L
 - Cl is <90 mEq/L
 - osmolality is <210 mOsm/L
 - urine total protein <20 mg/dL
 - β 2-microglobulin <4 mg/L
 - low fetal urine NAG and valine levels
- \ } tubule function
- / }
- \ } not leaking protein
- / }

After resolution of congenital obstruction, why is early renal fxn not always predictive of future fxn?

→ congenital obstruction not only affects nephrogenesis, but also subsequent nephron maturation

- nephron injury is heterogeneous } some nephrons undergo adaptive growth + hyperfiltration
- } other nephrons are destroyed
- GFR may be normal initially, despite significant reduction in functional renal mass
- with development of hyperfiltration nephropathy, remaining glomeruli undergo progressive sclerosis

HUMAN RELEVANCE

What is the difficulty in managing congenital urinary obstruction?

- determining who will need intervention to preserve renal functional development
- determining if intervention will make a difference
- determining when to intervene

What is wrong with the current definition of obstruction?

- “impairment of urine flow that will produce a reduction in renal function if left uncorrected”
- doesn’t address fact that neonatal kidney should be increasing in function, not remaining static
- should be “impairment of urine flow that has or will limit ultimate functional potential”

How does the captopril renogram demonstrate whether a dilated system is obstructed or not?

- obstructed kidney depends on increased activity of RAS for function
- reducing capacity of RAS to support renal function (via ACE inhibitor such as captopril)
in an obstructed kidney will result in drop in fxn (decreased radionuclide tracer uptake)

How can one prognosticate whether an intervention will improve the outcome of an obstructed kidney?

- we don’t have good prognostic tests that will guide therapy and influence risk-benefit analysis
- **we need to better determine which obstructed kidneys are at risk for developmental renal impairments and when to intervene**

Chapter #109 – Perinatal Urology

FETAL DIAGNOSIS

What are the significant urologic findings on prenatal U/S (CHART)?

→ **ALWAYS COMMENT ON AMNIOTIC FLUID VOLUME and FETAL SURVEY**

- 1) hydronephrosis } variable severity (unilateral vs bilateral)
 } obstruction vs VUR
 → variations in degree of hydro seen during U/S suggests VUR
 → **degree of hydro correlates poorly with postnatal outcome**
 → need to r/o cloacal anomaly and BOO if B/L obstruction in female fetus
 (usually also have retrovesical fluid-filled dilated vagina)
- 2) caliectasis } obstruction vs VUR
 → more indicative of significant pathology
- 3) hydroureter } looks like folded sausages between kidney and bladder
 } VUR, PUVs, ectopic ureters, ureterocele, and UVJO
- 4) pelvic AP diameter } measured in coronal plane
 } increased in obstruction and VUR
- 5) renal parenchyma } **should be less echogenic than liver & spleen**
 } echolucent medullary pyramids should be seen (starting at ~20wks)
 } **increased echogenicity in dysplasia, obstruction, and AR PCKD**
 } thin parenchyma in setting of hydro doesn't always mean decreased function
 → avoid the label "cortical atrophy"
- 6) urothelial thickening } may be thickened with obstruction and VUR
- 7) duplication } separation of renal pelvic sinus echoes when no hydronephrosis seen
 } possible associated VUR or obstruction
 } look for dilated ureter and ureterocele
- 8) renal cystic structures } large cysts (MCDK), multiple microcysts (AR PCKD)
 } **simple cysts are rare antenatally**
 → no communications between cysts (cf dilated calyces)
 → **single large UP cyst is likely a dilated UP moiety**
- 9) intravesical cystic structures } ureterocele (thin walled)
- 10) fluid collection around kidney } urinoma (perinephric or subcapsular)
 → sign of significant obstruction
- 11) bladder filling } assessment of urine production (fill and void cycles)
 → need to r/o exstrophy if unable to identify bladder on multiple U/S's
- 12) thickened bladder wall } obstruction vs neurogenic dysfunction
- 13) keyhole sign } dilated posterior urethra (hard to image)
 } PUVs
- 14) oligohydramnios } **reduced amniotic fluid with no pockets of fluid >2cm**
 } poor urine output due to obstruction vs renal failure

What is the normal appearance of the fetal kidney on prenatal U/S?

- elliptical shape with distinctive internal echoes defined by echolucent medullary pyramids
 → echolucent pyramids may be confused for dilated calyces
- uniform echogenicity of renal cortex
 → slightly less echogenic than liver and spleen

What is the significance of new oligohydramnios later in pregnancy?

- **OLIGOHYDRAMNIOS = amniotic fluid <500cc (pocket <2cm)**
- before 16-18 wks, most of AF is a placental transudate
- **by 20-22 wks, most of AF is fetal urine } urine production starts at ~12 wks**
- oligohydramnios that develops only after 18-20 wks likely represents GU tract obstruction or abN renal development (eg bilateral MCDK or AR PCKD)

What are the different ways to grade hydronephrosis?

- always denote side, whether bilateral or unilateral, and comment on pelvis & calyces
- correlation between degree of ante-natal hydronephrosis and postnatal outcome is POOR
- variations in degree of hydro during one exam is suggestive of VUR
- 1) descriptive } eg SFU system
- 2) quantitative } eg renal pelvic AP diameter scale

What is the SFU grading system of hydronephrosis in the fetus?

- Society of Fetal Urology consensus '98
- grade 0 } N kidney with no hydro
- grade 1 } slight splitting
 - slightly dilated renal pelvis WITHOUT caliectasis
- grade 2 } pelviectasis
 - moderately dilated renal pelvis with MILD caliectasis
- grade 3 } pelviectasis + caliectasis
 - large renal pelvis with dilated calyces and N renal parenchyma
- grade 4 } severe pelvicaliectasis + thinning of renal parenchyma
 - >50% thinning of contralateral kidney
- others have broken down grade 4 into 4a (segmental thinning) vs 4b (diffuse thinning)

What is the DDx of BILATERAL antenatal hydronephrosis?

→ **NORMAL TRANSIENT PHYSIOLOGIC FINDING IS MOST COMMON CAUSE !!!!!**

→ in order

1) **bilateral VUR (most common pathologic cause of bilateral antenatal hydro)**

2) PUV

3) bilateral UPJO

4) bilateral primary megaureter

5) prune-belly syndrome (VUR)

6) bilateral duplication with obstruction

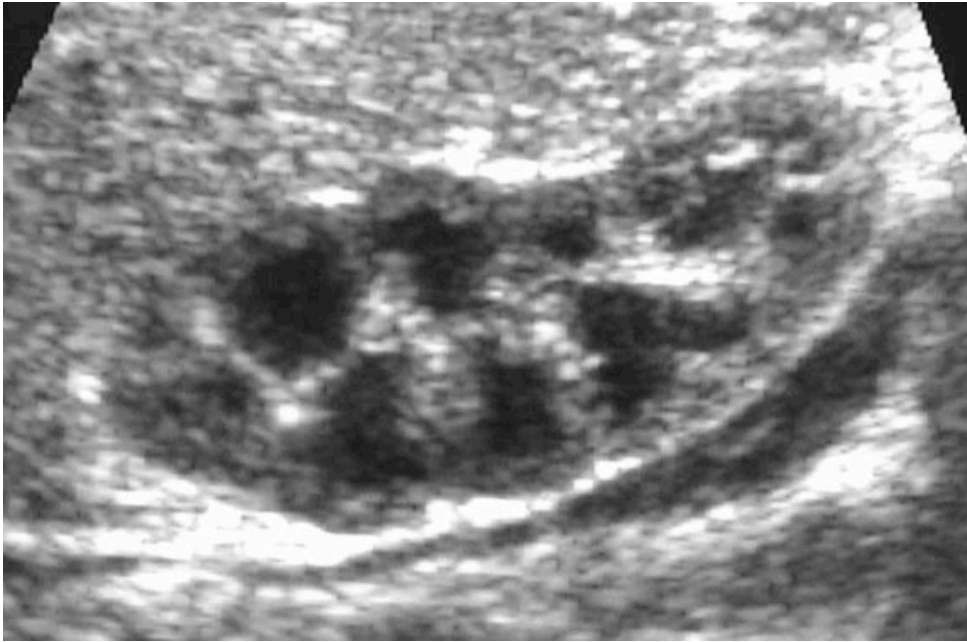
7) prolapsing ectopic ureterocele (causes BOO)

8) bilateral multicystic or AD PCKD

→ **UPJO is most common cause of UNILATERAL hydronephrosis**

What is the DDx of UNILATERAL antenatal hydronephrosis?

- **UPJO (most common → ~50%)**
- VUR
- UVJO
- dilatation of one unit of duplex kidney
- MCDK
- PUVs
- megaureter



→ NORMAL FETAL KIDNEY (echolucent medullary pyramids with more echogenic parenchyma)

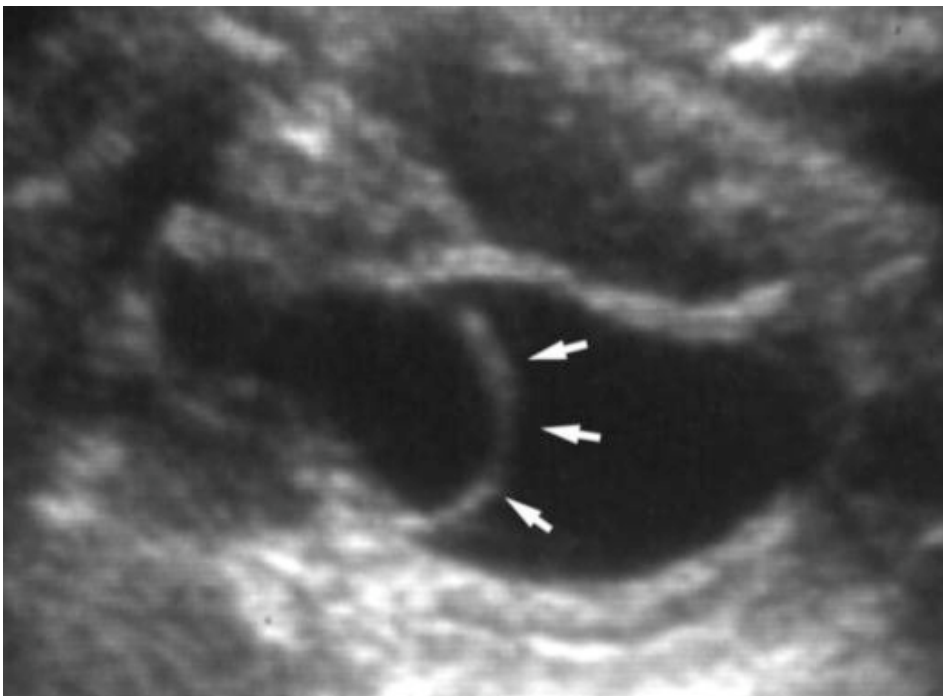


→ SEVERE FETAL HYDRONEPHROSIS

→ markedly dilated renal pelvis with diffuse caliectasis (communicating)



→ 22 WEEK OLD MALE WITH POSTERIOR URETHRAL VALVES
→ thickened bladder wall with dilated posterior urethra – “keyhole sign”

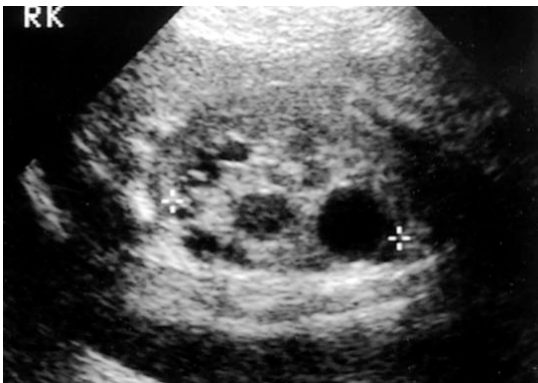


→ INTRAVESICAL URETEROCELE

What are the prenatal findings of some common urologic diagnoses?

- 1) UPJO
 - **some degree of pelvicaliectasis WITHOUT ureteral dilation**
 - usually unilateral but degree variable
- 2) UVJO
 - hydronephroureterosis to level of bladder
 - degree highly variable
 - hydroureter may be more significant distally
 - **need to r/o VUR**
- 3) VUR
 - variable degrees of dilation of collecting system
 - **no reliable way to predict presence of VUR nor its grade on basis of fetal U/S**
 - **variations in degree of hydro during exam suggests VUR**
 - massive B/L hydroureteronephrosis may be due to BOO but may also be due to VUR in the megacystis-megaureter association
- 4) PUVs
 - difficult fetal diagnosis
 - most severe manifestation may be seen as early as 13 wks
 - severe bladder distention + bilateral hydronephrosis + thickened bladder wall +/- perinephric urinoma +/- dilated posterior urethra +/- urinary ascites
 - associated increase in renal echogenicity may indicate renal dysplasia
 - **may start to see oligohydramnios by 18 wks**
 - T2 oligohydramnios is usually associated with early post-natal death due to associated pulmonary hypoplasia
 - late onset oligohydramnios (T3) is usually NOT associated with pulmonary insufficiency BUT may have obstetrical risks
 - **need to r/o bilateral megaureters & severe bilateral VUR**
- 5) ureterocele
 - intravesical thin-walled cystic structure
 - **more likely if presence of upper pole hydro + hydroureter to level of bladder**
 - absence of upper pole dilation SHOULD NOT exclude dx of ureterocele
 - may get “ureterocele disproportion” where UP becomes small & dysplastic with little ureteral dilation and only the ureterocele is visible
 - **single system ureteroceles are more common in boys**
 - **more likely orthotopic in boys**
 - BN prolapse of the ureterocele may cause bilateral hydro
- 6) ectopic ureter
 - UP hydronephrosis WITHOUT intravesical cystic structure
 - dilated ureter usually has thicker wall than found with ureteroceles
 - **usually seen w/ duplex system but can be rarely seen in B/L single system ectopia**
- 7) multicystic dysplastic kidneys (MCDK)
 - one of the most characteristic fetal U/S appearances
 - **non-reniform structure w/ multiple non-communicating fluid-filled cystic spaces + minimal to no recognizable parenchyma + no large central cyst**
 - cysts are of variable size
 - usually in normal renal position but can be seen in any position of an ectopic kidney
 - **MCDK usually becomes involuted**
 - **often confused with severe hydronephrosis** (large central cystic space w/ communication between similarly-sized cystic spaces)
 - absence of communication between cystic spaces is key to Dx
 - duplex systems may include an UP multicystic dysplastic moiety
- 8) AR PCKD (aka “infantile PCKD”)
 - usually develops before 20 wks
 - **see B/L enlarged, brightly echogenic kidneys WITHOUT grossly visible cysts**
 - associated with various mutations on the PKHD1 gene on **chromosome 6p12**
 - high neonatal mortality due to **pulmonary insufficiency** from Potter’s syndrome
 - those that survive progress to renal and **liver failure**

- 9) Bilateral renal agenesis
 - see a progressive absence of amniotic fluid after 16-18 wks
 - **no detectable kidneys + absence of bladder filling**
 - adrenal glands seen in normal position but are linear ("lying down adrenal")
 - **Potter's syndrome** } oligohydramnios + lung hypoplasia + skeletal defects + low set ears
 → lethal neonatal pulmonary insufficiency
- 10) Bladder exstrophy
 - **absence of bladder filling on repeated exams**
 - **low-set umbilical cord**
 - protuberance of tissue from lower abdomen
 - **abN looking external genitalia**
 - **normal kidneys and associated extraurinary abN's are uncommon**
 → unlike cloacal exstrophy which is often associated with myelomeningocele, lower extremity abN's, and cardiac defects
- 11) penile anomalies
 - hypospadias, severe chordee, epispadias, etc
 - need to look for testes to determine sex of fetus
 - may need karyotyping via amniocentesis
 → **without identification of testes, cannot assign sex**
 → may be female fetus with CAH (virilization - enlarged clitoris)
- 12) Cloacal malformation
 - bilateral hydronephrosis + enlarged bladder + retrovesical fluid-filled vagina
 - get BOO from distended vagina



→ MULTICYSTIC DYSPLASTIC KIDNEY

→ multiple non-communicating fluid-filled cystic spaces, of variable size, with minimal to no recognizable renal parenchyma and no central large cyst

What is the DDX of a multicystic kidney?

- 1) **MCDK (variable sizes) } most common**
- 2) AD PCKD (usually large cysts)
 → unlike AR PCKD which is has large uniformly echogenic kidneys WITHOUT recognizable cysts
- 3) congenital multilocular cystic nephroma (variably sized macrocysts)
- 4) cystic Wilms' tumour
 → usually have larger amounts of parenchyma
- 5) severe hydronephrosis
- 6) nonrenal cystic lesions
 - mesenteric duplication cysts
 - neurenteric cysts
 - bronchogenic cysts
 - extrathoracic pulmonary sequestration
 - cystic neuroblastoma

What other findings on fetal U/S are associated with GU anomalies?

- Down's syndrome } increased nuchal fold thickness
 } 3% of fetuses with hydro have Down's
- cardiac mass (rhabdomyosarcoma) } often assoc'd w/ TS and possible renal masses (AMLs)

What is the DDx of a solid “renal mass” seen on FETAL U/S?

→ renal masses are unusual in fetal GU tract

1) congenital mesoblastic nephroma (most common)

- benign tumour that usually replaces entire kidney with homogeneous round mass
- may be associated with **polyhydramnios**
- can't r/o malignancy so early post-natal removal is recommended

2) neuroblastoma

- may appear as renal mass or cystic suprarenal masses
- prenatal MRI can help with Dx
- need to r/o metastatic neuroblastoma } total body examination needed

3) Wilms' tumour

- rarely described prenatally

What is the Ddx of a persistently dilated bladder on antenatal U/S?

- PUVs
- prune belly syndrome
- obstructing ureterocele
- urethral atresia
- anterior urethral valves

What features on antenatal U/S are associated with the highest risk of pulmonary hypoplasia?

- 1) oligohydramnios
- 2) male
- 3) hydronephrosis
- 4) dilated bladder
- 5) dilated posterior urethra (keyhole sign)

What is the DDx of POLYHYDRAMNIOS on prenatal U/S?

- congenital mesoblastic nephroma
- TE fistula
- duodenal atresia
- anencephaly
- gastroschisis
- omphalocele
- maternal DM

PATHOPHYSIOLOGY OF CONGENITAL OBSTRUCTION

What are the 3 most important concepts regarding prenatally detected congenital obstructive uropathy?

- 1) congenital obstruction is different from postnatal obstruction
 - affected kidney is undergoing rapid growth and development
 - kidneys are not the only filtration system for the fetus (maternal placenta)
- 2) consequences of renal dysfunction in utero are unique to the fetal environment
 - still get filtration from mother via placenta
 - renal dysfunction results in oligohydramnios +/- Potter's syndrome
 - pulmonary hypoplasia a result of abN development & maturity (bronchial branching) due to lack of AF
 - **late onset (>30 wks) oligohydramnios is not associated w/ pulmonary hypoplasia**
 - adequately developed lungs do not reverse and become hypoplastic
- 3) incidence of certain prenatally detected uropathies are markedly sex specific
 - hydronephrosis is 4-5x more common in males
 - VUR more common in boys (4fold higher)
 - likely a result of different developmental patterns of the male rhabdosphincter

How does congenital obstruction affect the developing fetal kidney?

- 1) smaller size (hypoplasia)
- 2) change in differentiation cells (leads to "dysplastic" kidney)
- 3) increased RAAS activity
- 4) injury response patterns seen (fibrosis, inflammation)
- 5) develop nephrogenic DI
- 6) get associated pulmonary hypoplasia

MANAGEMENT OF FETAL UROPATHIES

How common are fetal GU tract anomalies?

- 0.2 to 1.5% of all pregnancies } >50% are due to some form of hydronephrosis
- **UPJO is most common cause of unilateral fetal hydronephrosis**
 - also common are VUR, PUVs, and megaureter
- only ~5% of all prenatally diagnosed uropathies require fetal intervention

What antenatal U/S features that are predictive of a poor functional prognosis?

- 1) early hydronephrosis (present at <24wks)
- 2) oligohydramnios
- 3) bilateral moderate to severe hydroureteronephrosis (APD ≥10-15mm)
- 4) evidence of dysplasia (echogenic cortex, microcystic renal changes)
- 5) thick-walled, dilated bladder detected early (in male)

What is the natural history of antenatal hydronephrosis?

- **poor correlation b/w degree of antenatal hydro & postnatal outcomes** } most resolve
- mild hydronephrosis + normal-appearing parenchyma } further prenatal f/u recommended but is seldom useful
- more severe unilateral hydronephrosis or B/L hydronephrosis } prenatal f/u recommended
- severe B/L hydronephrosis with suspicion of BOO } regular prenatal f/u indicated
 - } need to f/u on the AF volume, renal echogenicity, and presence of any extra-renal fluid collections

List indications & conditions for in utero decompression for obstructive uropathy (CHART)

- fetal intervention only indicated when life of neonate is at risk
- also essential that no other life-threatening conditions exist (mainly CV and neurologic)
- should be a reasonable chance that in utero decompression of the bladder will be beneficial

➔ “BUMKINNES”

- 1) presumed **BOO** with severe bilateral hydronephrosis & oligohydramnios
- 2) Urinary indices are favorable, or serial samplings trending toward normal
 - Na <100 (sodium retention)
 - Cl <100
 - Osm <210 (excretion of free water)
 - β 2-microglobulin <10-20
- 3) Male fetus
- 4) Karyotype is N by amnio
- 5) Informed consent
- 6) No systemic anomalies
- 7) Non-cystic kidneys (cysts are poor prognostic sign)
- 8) relatively Early onset oligohydramnios (20-25 wks)
- 9) Singleton

What is the current fetal intervention for BOO?

- started at UCSF } double pigtail vesicoamniotic shunt (Harrison et al, '82)
 - now a Rodeck shunt is placed under U/S guidance } +/- amnioinfusion for fetal visualization
 - sometimes fetus must be paralyzed
- endoscopic fetal intervention has emerged as a new option but likely doesn't provide enough decompression needed in a fetus with severe urinary compromise

How successful are vesicoamniotic shunts?

- survival is increased BUT many still have renal insufficiency & pulmonary impairment
 - 3 initial studies w/ long-term outcomes (Freedman et al '00, Holmes et al '01, Biard et al '05)
 - ~60% have renal insufficiency & ~85% had growth impairment
 - more recent f/u studies show better results
 - ~65% had N function or mild renal impairment } better outcome w/ prune-belly
 - } worst outcomes w/ urethral atresia
- **ideal time is >20 wks but before 32 wks** } oligo before 20wks usually incompatible w/ life
 } early delivery preferable if >32 wks
- **high risk of complications and prenatal mortality is high** } **40-50%**

What are the potential complications of prenatal vesicoamniotic shunts?

- chorioamnionitis
- damage to adjacent structures
- premature labour
- stent occlusion
- stent displacement
- intestinal hernia through stent site

POSTNATAL EVALUATION AND MANAGEMENT

What is the evaluation of the pt with antenatally detected hydronephrosis?

- 1) History
 - maternal health
 - maternal PMHx & FmHx } GU anomalies, course of pregnancy, DM, Meds
 - previous pregnancies } siblings w/ VUR, hydro
 - sex of child
 - EtOH, drug use
- 2) Examination
 - fundus appropriate for gestation
 - BP
- 3) pre-natal U/S
 - **Gender of fetus**
 - Single vs. multiple
 - AF volume
 - Kidneys } degree of hydro, variation in hydro b/w exams, unilateral/bilateral hydro, parenchymal thickness/echogenicity, extrarenal collections, etc
 - Ureters } hydroureter
 - Bladder } presence, fullness, size, thickness, emptying
 - Urethra } dilated posterior urethra
 - Other abnormalities
 - Overall growth and development

Table 109-3 -- Postnatal Management Scheme for Hydronephrosis

Prenatal Findings	Early Antibiotics	Imaging	Timing	Possible Diagnoses	Surgery
Mild hydronephrosis	No	RUS	2 to 3 months	Mild UPJO	Unlikely
		VCUG (controversial)		Mild UVJO Reflux	
Moderate to severe hydronephrosis	Yes	RUS	1 to 2 months	Moderate UPJO	Unlikely
		VCUG		Moderate UVJO Reflux	
				Valves, mild	
Severe unilateral hydronephrosis	Yes	RUS	1 month	UPJO	Possible
		VCUG		UVJO Reflux	
		IVP/MAG3		Valves (unusual)	
Severe bilateral hydronephrosis	Yes	RUS	<1 week	Reflux Valves	Probable
		VCUG		Bilat UPJO	
				Bilat UVJO	
Intravesical cystic structure	Yes	RUS	<1 month	Ureterocele	Likely
		VCUG			

What is the management of a child with antenatally detected hydronephrosis?

- 1) Unilateral
 - a) Antenatal } observe, reassure, investigate postnatally
 - b) Post-natal
 - rarely any indication for urgent investigation if N contralateral kidney
 - normal oliguria/dehydration of neonate may under-represent degree of obstruction or likelihood of reflux so better to wait
 - baseline serum Cr by day 2-3 } not immediately as it may reflect maternal renal function
 - mild } no ABx, U/S in 2-3 months, +/- VCUG
 - mod to severe } ABx, U/S at 1-2 months + VCUG (if hydro persists)
 - severe } ABx, U/S at 1 month, VCUG at 1 month (if hydro), MAG3 (if VUR)
- 2) Bilateral
 - a) Antenatal } look at AF volume + bladder volume
 - Normal AF volume
 - enough renal function to allow N lung development
 - **U/S every few weeks } ensure AF volume remains N**
 - consider induction if decreasing AF volume } may impair lung maturation
 - Oligohydramnios
 - If N lung development } observe ± early induction
 - amniotic fluid Lecithin:Sphingomyelin ratio > 2:1
 - If abN lung development (L:S < 2:1)
 - a) + other associated fatal anomalies } consider termination
 - b) no assoc'd anomalies } steroids to induce lung maturation + early delivery
 - c) fetal intervention controversial and rarely needed
 - b) Post-natal
 - observe child voiding
 - serum Cr, U/A
 - prophylactic ABx } amoxil, TMP alone
 - **U/S on 1st day of life if concerned about PUV**
 - PUV } palpable mass, neonatal ascites, thick bladder wall
 - keep in mind neonatal dehydration may underestimate problem
 - **U/S w/in 1 wk if severe but not concerned about PUV, otherwise at 1-2 mos**
 - only mild fullness } follow with serial U/S
 - moderate fullness } VCUG + serial U/S
 - severe hydro } VCUG, serial U/S, MAG3 or DTPA lasix scan
 - if no hydroureter, UPJO likely } more elective evaluation ok
 - **VCUG w/in 1 wk if severe bilateral hydro, otherwise 1-2mo**
 - if PUV suspected, bladder catheter left in situ until definitive therapy
 - 5F feeding tube
 - consider valve ablation vs. vesicostomy
 - proximal diversion if persistent hydro, ↑d Cr, acidosis @ day 3-5

What is the controversy surrounding VCUG for hydronephrosis?

- controversial as to who gets VCUG } some say all with antenatal hydro
 - } others use an arbitrary cutoff (eg calyceal dilation or >7-10mm AP pelvic diameter)
- **poor correlation between hydronephrosis severity & grade of reflux**

What is the controversy surrounding renal functional imaging of obstructive conditions?

- imaging serves the purpose of determining the need for and timing of intervention
- can't set guidelines as to who should get functional imaging studies because there is significant controversy as to how to interpret the results in infants
- arbitrary thresholds are used
 - levels of AP pelvis diameter
 - presence of calyceal dilation
 - degree of pelvic and ureteral dilation
- lasix renal scans preferred over IVP
- role of nuclear VCUG is also controversial

What is the role of functional imaging for VUR?

- likely useful when VUR is present
 - high incidence of abN scans even in the absence of infections
 - markedly abN scans especially with high grade reflux in boys
 - also have high degree of associated abN urodynamic patterns

What are the VCUG features of PUVs?

- 1) dilated posterior urethra
- 2) elongated posterior urethra
- 3) abrupt caliber change
- 4) trabeculated bladder
- 5) hypertrophied bladder neck
- 6) VUR

What is the initial management of PUVs?

→ **early VCUG to confirm Dx**

→ diligent f/u of renal and bladder function is critical

- 1) bladder drainage (permits medical stabilization until decision made about Rx)
 - if PUV suspected, immediate placement of urinary catheter drainage of bladder req'd
 - 3.5 or 5Fr feeding tubes in neonates
 - consider one-shot cystogram to confirm placement
 - may be difficult to get catheter over elevated BN and avoid coiling in dilated prostatic urethra
- 2) effective NICU support for issues with pulmonary hypoplasia & renal insufficiency
 - ventilatory support, ECMO, dialysis, TPN, BP control, etc
- 3) prophylactic ABx
- 4) valve ablation
 - permanent ablation of PUV once stable
 - **preferred initial surgical treatment**
 - cystoscopic ablation via bugbee electrode, resectoscope, cold knife incision, laser incision, etc
 - goal is not to resect entire valve } higher complication rate
 - incisions at 12-, 4- and 8-o'clock, or all 3 sites
 - leave catheter in place for 24hrs post incision
- 5) cutaneous vesicostomy
 - **if neonate is too small or too sick for safe instrumentation for PUV ablation,** cutaneous vesicostomy can be used as a temporary measure
 - provides adequate drainage & preserves renal function } comparable to primary valve ablation
 - doesn't affect bladder capacity
 - some report that compliance is decreased
- 6) proximal diversion vs total early reconstruction if persistent hydro or azotemia
 - creatinine persistently elevated (>180) after ~10days
 - issue w/ proximal diversion is the long-term effects of bladder decompression
 - issue w/ total early reconstruction is ability to reimplant ureters & achieve closure

What is the recommended postnatal management of megacystis-megaureter?

→ massively dilated bladder + B/L hydroureteronephrosis + B/L VUR

→ **resembles PUV but bladder is usually thin walled & smooth**

1) **prophylactic ABx**

→ may present with pyelo/sepsis

2) **observation in some, but most require Sx** (recurrent UTIs or deteriorating renal function)

→ excisional megaureter tailoring + ureteral reimplantation

→ little to **no indication for cutaneous vesicostomy**

→ different from megaureter } Rx is ABx and observation in most

What is the recommended postnatal management of MCDK?

- **usually unilateral isolated finding with good prognosis**

→ multiple, fluid-filled spaces of varying size, w/o communication or large central cyst

- **ensure N contralateral kidney**

→ **increased frequency of VUR and UPJO of contralateral kidney reported**

- role of VCUG controversial

- **DMSA renal scan is best test to confirm Dx**

→ no uptake if MCDK

- need for surgical removal is also controversial } most recent data shows little to no ↑'d risk of Wilms

What is the recommended postnatal management of AR PCKD?

- typically bilateral with lethal outcome due to pulmonary failure

→ symmetrically large kidneys with reniform shape

→ multiple small cysts giving uniformly bright echogenic sonotexture

- role of screening for affected gene (PKHD1 on chromosome 6p12)

- **management depends largely on pulmonary capacity**

→ peritoneal dialysis if sufficient lung capacity

What is Caroli's disease?

- AR PCKD that presents with large echogenic cystic kidneys with slower deterioration of renal function

- live long enough to develop hepatic & pancreatic cystic disease

NEONATAL UROLOGIC EMERGENCIES

What are some presenting signs of neonatal urologic emergencies (CHART)?

1) Sepsis } BOO (PUV or neurogenic), VUR, megaureter, ectopic ureter, ureterocele, UPJO,
fungal infection + secondary infection

→ urine and blood C&S, U/S, VCUG

2) hematuria } UTI, RV thrombosis

→ urine C&S, U/S

3) HTN } RV thrombosis, RA thrombosis

→ U/S, DMSA scan

4) renal mass } hydronephrosis, AR PCKD, MCDK, congenital megaloblastic nephroma,
neuroblastoma, Wilms' tumour

→ U/S, CT scan, DMSA scan, MRI

5) renal failure } obstruction, sepsis, renal cortical necrosis, renal dysplasia, renal agenesis

→ urine C&S, urine lytes, U/S, DMSA or MAG3 scan

6) urinary ascites } obstruction

→ U/S

7) scrotal mass } neonatal torsion, hydrocele, tumour

→ U/S

What is the DDx of a perineal mass in a NEWBORN girl?

- 1) **benign periurethral cyst (most common)**
 - whitish in appearance and covered by a delicate but N epithelium
 - adjacent urethral meatus is uninvolvedRx → I&D
- 2) imperforate hymen with hydrocolpos
 - midline bulge of whitish tissue symmetrically between the labia and behind the urethra
 - may have palpable lower abdo mass (distended uterus)
 - can get associated hydro from secondary BOO } retrovesical fluid filled cavityRx → I&D
- 3) prolapse of ectopic ureterocele
 - similar to hydrocolpos but is often edematous, congested, or frankly necrotic
 - seen emerging from urethra in an eccentric fashion (usually posteriorly)
 - distended bladder may be palpable
 - may also have palpable hydronephrotic kidneyRx → U/S, VCUG, renal scan
→ incision of ureterocele + Foley drainage of bladder
- 4) urethral prolapse (uncommon in newborns)
 - more common in pre-pubertal black F & post-menopausal F
 - circumferential collar of edematous and ecchymotic tissue at urethral meatusRx → skin moisturizer, hot compresses
→ relief of aggravating factors (catheter, prolonged coughing, straining)
→ if tissue necrosis is evident, surgical resection is required
- 5) botryoid rhabdomyosarcoma of the vagina (uncommon in newborns)
 - uncommon in neonate
 - multilobulated appearance with evidence of a solid pelvic mass

What is the DDx of an abdominal mass in a neonate (CHART)?

- **GU tract (~70%)**
- **MCDK** (most common single entity)
 - **hydronephrosis** (PUV, urinary duplication and ectopia, UPJO) } hydro is the most common overall entity
 - AR/AD PCKD
 - RV thrombosis
 - Wilms' tumour
 - **congenital mesoblastic nephroma (most common renal tumour in neonate)**
 - distended bladder
- **non-GU tract (~30%)**
- **neuroblastoma (most common extra-cranial tumour in kids)**
 - teratoma
 - GI duplication
 - adrenal hemorrhage
 - hydrometrocolpos
 - ovarian cysts
 - giant cystic meconium ileus

What is the management of imperforate anus?

- **high frequency of assoc'd GU anomalies**
→ potential for fxn'ly significant neurologic bladder dysfxn
→ **presence of punctate calcifications in intestinal lumen (due to meconium calcifications that form from exposure to urine) may suggest imperforate anus**
- 1) U/S + VCUG } assess GU tract & also identify level of recto-urethral/vesical fistula in boys
 - 2) watch for complications related to confluence of GI and GU tracts
→ infection & metabolic derangements
 - 3) must r/o spinal cord abN's } especially spinal cord tethering
 - 4) diverting colostomy using transverse colon with separation of proximal and distal limbs
→ delayed reconstruction

What are the features of Potter's syndrome?

→ **usually die from respiratory failure in first few hrs of life**

- oligohydramnios
- limb contractures (especially clubfeet)
- compressed flat facies
- low-set ears
- absent, bilaterally dysplastic or bilaterally cystic kidneys on U/S

Rx → supportive care

→ counseling of parents

What GU anomalies are associated with single umbilical artery?

→ usually 2 arteries and 1 vein

- renal anomalies (7%) } usually of minimal significance
- VUR (4.5%)

→ routine screening not recommended

What is the management of pediatric urosepsis?

- resuscitation
 - catheterized or S/P aspirated urine C&S } before initiating Abx
 - Abx
 - U/S } most cases have an abN result
 - VCUG } normal U/S does not r/o VUR
- further w/u tailored towards findings
- higher risk of urosepsis in uncx'd boys

What is the significance of a child that has not voided?

- timing is everything
- normal time for 1st post-natal void can extend to >24hrs
- must look for distended bladder
- U/S if delayed onset of micturition
- time to voiding after Cx is predictable } most void within 8hrs of Cx

What is the management of hematuria in the newborn?

- usually benign
 - could be due to withdrawal of maternal hormones resulting in benign urethral bleeding NYD
 - physical examination, urine C&S, and U/S
- **r/o RV thrombosis, stones, UTI**

What is the management of ambiguous genitalia?

- history } drugs during pregnancy, previous pregnancies, unexplained deaths, etc
- P/E } phallic and scrotal structures, pigmentation, presence of gonads, abdo masses, DRE
- investigations } "FUUKED Large, Then Gone After 17"
 - FSH
 - U/S
 - Urine for 17-ketosteroids
 - Karyotype
 - Electrolytes
 - DHT
 - LH
 - Testosterone
 - Genitogram (later)
 - Anti-mullerian hormone (MIS)
 - 17-OH-progesterone & DOC
- do not assign gender
- multi-disciplinary approach with family

What is the management of neonatal UDT?

- unilateral } observation
 - } delay Rx for ~3-6 months (75% down by 3mos)
- bilateral } r/o intersex condition
 - "FUUKED Large, Then Gone After 17"

What is the management of neonatal swollen scrotum?

- r/o hydrocele (transillumination)
- U/S
- exploration to r/o incarcerated testes } contralateral fixation

What is the management of bladder exstrophy?

- assess genital structures, location of testes, size of bladder plate
- renal U/S
- protect bladder with plastic wrap (no Vaseline)
- plan early closure } refer to tertiary care hospital

What is the management of a patent urachus?

- U/S to r/o cystic urachus
- VCUG to r/o associated bladder anomalies (obstruction)

What is the management of neonatal myelomeningocele?

- baseline U/S and VCUG as soon as possible
- start CIC
- early anti-cholinergic therapy

SPECIFIC DIAGNOSES

Renal Vein Thrombosis

How does RV thrombosis present in the neonate?

- child usually **DOES NOT look sick**
- enlarged kidneys (20% of neonates have B/L involvement)
- **hematuria** (20% of all neonates with gross hematuria – most common cause in neonatal hematuria)
- anemia
- thrombocytopenia
- hx of prolonged delivery
- prematurity
- up to 50% have prothrombotic abN's } **should be screened for coagulation abN'ities**
- **U/S is best for making the Dx**

List RFs associated with renal vein thrombosis in a child } } } “Premature SPUD CANT Dance”

- | | |
|------------------------------------|--|
| - Prematurity | - Coagulopathies (eg antithrombin-3 or protein C deficiencies) |
| - Sepsis | - Asphyxia |
| - Polycythemia | - Nephrotic syndrome |
| - Umbilical artery catheterization | - Trauma/Tumour |
| - Dehydration | - DM mothers |

What is the cause of neonatal RV thrombosis?

- impaired RBF in the setting of a neonate w/ normally low BP, polycythemia, & dehydration
eg CAH, salt wasting
- **thrombosis is peripheral & usually does not propagate centrally**

What is the management of RV thrombosis?

- rehydration
- correction of secondary electrolyte imbalances
- anticoagulation with heparin or fibrinolytics (streptokinase) } **CONTROVERSIAL**
→ treatment with heparin associated with less renal functional abN'ities
- if bilateral RV thrombosis, more aggressive Rx is needed to prevent ESRD

Renal Artery Thrombosis

How does neonatal renal artery thrombosis usually present?

- HTN
- hematuria
- **hx of umbilical artery catheterization } most common cause**
- renal insufficiency
- proteinuria
- CHF
- may have thrombotic involvement of the aorta
- Dx made by U/S

What is the management of renal artery thrombosis?

- unilateral } expectant management
- } thrombolytics may be appropriate
- bilateral } thrombolytics
- control of HTN is most important
- Nx for non-functional kidney may be required

What is the DDx of HTN in a neonate?

- renal artery thrombosis
- coarctation of aorta
- hyperaldosteronism
- neuroblastoma
- adrenal syndromes

Adrenal Hemorrhage

How does neonatal adrenal hemorrhage usually present?

- anemia
- shock
- abdominal mass
- scrotal hemorrhage
- gross hematuria is rare
- U/S best for making Dx } may need to do MRI to r/o neuroblastoma
- } may see calcifications in involuting mass as early as 1 wk

What are the RFs for adrenal hemorrhage in the neonate?

- relatively common } 1-2% of healthy infants
- prolonged labour
- birth trauma
- large birth weight

How can you differentiate an adrenal hemorrhage from a neuroblastoma on imaging?

- **adrenal hemorrhage } peripheral eggshell calcifications** (like Wilms tumour)
- neuroblastoma } stippled calcifications

What conditions are associated with adrenal hemorrhage in the neonate?

- renal vein thrombosis
- Beckwith-Weideman syndrome

What is the management of adrenal hemorrhage in a neonate?

- supportive and expectant } need for intervention is rare

Chapter #110 – Evaluation of the Pediatric Urology Patient

TRIAGE OF THE PEDIATRIC UROLOGIC PATIENT

What are the 4 main triage categories for pediatric patients (CHART)?

1) emergent } needs to be seen immediately

- trauma
- suspected child abuse
- acute post-op complication
- newborns w/ B/L hydro or hydro in a solitary kidney
 - need to r/o PUV in males
- newborns w/ gross hematuria or UTIs
 - gross hematuria may indicate renal artery thrombosis or renal vein thrombosis (RV thrombosis is more common in males 2:1 and is usually on L side)
 - febrile UTIs have high association with bacteremia (10-20%) and can result in significant renal scarring if not treated
- newborns with ambiguous genitalia, bladder or cloacal exstrophy, PUVs, prune-belly syndrome, urethral atresia or spina bifida
 - ambiguous genitalia may be due to CAH (can get life threatening salt wasting)
 - 1/3 of infants w/ PUVs or prune-belly will develop pulmonary insufficiency
 - all kids needing neuroSx for spinal dysraphism must be assessed for bladder dysfxn or VUR (ie U/S + VCUG + UDS once post-op spinal shock gone)
- kids with acute abdominal or acute scrotal pain
 - need to r/o GI cause, torsion, UPJO, stone, constipation, UTI
 - 60% of neonatal abdo masses are GU in origin (neuroblastoma most common)
- boys with priapism

2) urgent } need to be seen within 24hrs

- gross hematuria outside newborn period
- stones
- febrile UTI outside newborn period (if not treated will result in renal scarring)

3) semi-urgent } need to be seen in 48-72hrs

- postnatal evaluation of prenatal unilateral hydro (no evidence of BOO, renal dysfxn, oligohydramnios, or significant cystic renal disease in fetus <22wks)
- symptomatic hernia or hydrocele
 - need to r/o incarcerated hernia
- failure to thrive
- amenorrhea in adolescent female
 - need to r/o imperforate hymen or uterine anomalies
- nonfebrile UTI outside newborn period
 - all should get U/S and VCUG +/- renal scan

4) routine } next most convenient time

- asymptomatic hernia or hydrocele
- Cx evaluation (as long as child is voiding normally, no urgency)
- hypospadias
- undescended testes
- varicocele
- VUR
- microscopic hematuria
- enuresis (daytime symptoms usually more bothersome than nocturnal enuresis)

What are some chromosomal syndromes associated with GU anomalies?

Chromosome #	clinical features	Renal anomalies	Genital anomalies
Warkany syndrome (trisomy 8)	- large, square head - prominent forehead - hypertelorism	- hydronephrosis - horseshoe kidney - VUR	- hypospadias - UDT
9p trisomy, monosomy, tetrasomy	- small cranium - strabismus - large nose - webbed neck	- renal hypoplasia - pancake kidney	- hypospadias - UDT - infantile male genitalia
10q, 10p syndrome	- microcephaly - oval, flat face - microphthalmia	- hydronephrosis - cystic kidney	- UDT - small penis
Patau's syndrome (trisomy 13)	- hypertelorism - polydactyly - congenital heart disease	- hydronephrosis - horseshoe kidney - cystic kidneys	- UDT
Prader-Willi syndrome (monosomy 15q11)	- obesity - retardation		- UDT
Edward's syndrome (trisomy 18)	- hypertonia - congenital heart dz	- hydronephrosis	- small penis
Down's syndrome (trisomy 21)	- retardation - congenital heart dz - nasal hypoplasia - broad, short hands		- UDT - small penis
Cat's eye syndrome (trisomy 22)	- anal atresia - beaked nose - cleft palate - coloboma	- horseshoe kidney - renal agenesis - VUR	- UDT - small penis
Klinefelter's syndrome (XXY)	- elongated legs - gynecomastia - eunuchoid body - sparse body hair		- small penis - small testes
Turner's syndrome (XO)	- short stature - primary amenorrhea - webbed neck - broad chest - coarctation of aorta	- horseshoe kidney	- infantile genitalia

Which syndromes (with multisystem disease) are associated with CRYPTORCHIDISM?

Syndrome	Renal anomaly	Genital anomaly	Other anomalies
Cerebro-oculo-facial (AR inheritance)	- renal agenesis	- UDT	- microcephaly - cataracts
Marfan syndrome (AD inheritance)	- renal duplication - hydroureter	- UDT	- aortic aneurysm - arachnodactyly
Meckel-Gruber syndrome (AR inheritance)	- renal cysts	- UDT - ambiguous genitalia	- microcephaly
Menkes syndrome	- hydronephrosis - VUR	- UDT	- CNS abN's - kinky hair
Prader-Willi syndrome		- UDT	- hypotonia - obesity - mental retardation
Prune-belly syndrome	- hydronephrosis	- UDT	- hypoplastic abdo muscles
Robinow syndrome		- small genitalia - UDT	- flat face w/ short forearms
Zellweger syndrome (AR inheritance)		- UDT - hypospadias	- hypotonia - hepatomegaly

Which syndromes (with multisystem disease) are associated with HYPOSPADIAS (49 in total)?

Syndrome	Renal anomaly	Genital anomaly	Other anomalies
VACTERL syndrome	- renal dysplasia - hydronephrosis	- hypospadias	- vertebral anomalies - anal atresia - cardiac anomalies - TE fistulae - limb defects
Dubowitz syndrome (AR inheritance)		- hypospadias - UDT	- eczema - small stature
Fraser syndrome		- hypospadias - UDT	- cryptophthalmos
Opitz syndrome (AR inheritance)		- hypospadias - UDT	- hypertelorism - mental retardation
Robert syndrome (AR inheritance)	- hydroureter	- hypospadias - large penis - UDT	- hypomelia - growth retardation
Smith-Lemli-Opitz (AR inheritance)		- hypospadias - Udt	- pernicious anemia - mental retardation
Zellweger syndrome (AR inheritance)		- hypospadias - UDT	- hypotonia - hepatomegaly

Which syndromes (with multisystem disease) are associated with RENAL AGENESIS?

Syndrome	Renal anomaly	Genital anomaly	Other anomalies
Caudal regression	- renal agenesis - hydronephrosis	- vaginal and uterine agenesis	- imperforate anus - LS spine abN
Curran syndrome	- renal agenesis		- acral anomalies
Mayer-Rokitansky syndrome	- renal agenesis	- duplex uterus - vaginal atresia	
Cerebro-oculo-facial (AR inheritance)	- renal agenesis	- UDT	- microcephaly - cataracts
VACTERL syndrome	- renal dysplasia - hydronephrosis	- hypospadias	- vertebral anomalies - anal atresia - cardiac anomalies - TE fistulae - limb defects

Which syndromes (with multisystem disease) are associated with WILMS' TUMOUR or RCC?

Syndrome	Renal anomaly	Genital anomaly	Other anomalies
Beckwith-Wiedemann	- Wilms' tumours		- macroglossia - gigantism
Denys-Drash syndrome	- Wilms' tumour - GN	- mixed gonadal dysgenesis	
VHL syndrome	- RCC - renal cysts		- pancreatic cysts - cerebral hemangioblastoma - retinal angiomas - pheochromocytomas - endolymphatic sac tumours
WAGR syndrome	- Wilms'	- GU anomalies (gonads)	- aniridia, retardation

Which syndromes (with multisystem disease) are associated with SMALL GENITALIA?

Syndrome	Renal anomaly	Genital anomaly	Other anomalies
CHARGE syndrome		- small genitalia	- coloboma - heart defects - anal atresia - retardation - genetic and ear anomalies
Laurence-Moon-Biedl syndrome		- small genitalia	- obesity - retinal pigmentation
Carpenter syndrome (AR inheritance)		- small genitalia	- acrocephaly - polydactyly

What is the DDX of recurrent abdo pain in kids (CHART)?

- 1) non-organic } recurrent abdo pain syndrome
 } IBS
 } nonulcer dyspepsia
- 2) GI tract } chronic constipation
 } lactose intolerance
 } parasite infection (especially Giardia)
 } excess fructose or sorbitol ingestion
 } Crohn's disease
 } PUD
 } esophagitis
 } Meckel's diverticulum
 } recurrent intussusception
 } internal, inguinal, or abdo wall hernia
- 3) GB and pancreas } gallstones
 } choledochal cyst
 } recurrent pancreatitis
- 4) GU tract } UTI
 } hydronephrosis
 } stones
 } other GU disorders
- 5) miscellaneous } abdominal migraine
 } abdominal epilepsy
 } Gilbert's syndrome
 } Familial Mediterranean fever
 } sickle cell crisis
 } Lead poisoning
 } Henoch-Schonlein purpura
 } angioneurotic edema
 } acute intermittent porphyria

What are the causes of gross hematuria in kids outside the newborn period?

→ renal vein thrombosis is most common cause of gross hematuria in neonate

- UTI (~25%)
- perineal irritation (~10%)
- trauma (7%)
- urethral prolapse
- meatal stenosis with ulceration (7%)
- abnormal coag's (3%)
- stones (2%)
- acute nephritis } post-streptococcal GN & IgA nephropathy most common
- UPJO
- epididymitis
- tumour

What is the DDX of a mass at the introitus (interlabial) of an infant girl?

- benign periurethral cyst (most common cause in neonate)
- imperforate hymen with hydrometrocolpos (neonatal or pubertal)
- prolapsed ureterocele } **may cause BOO**
- prolapsed urethra (uncommon in newborn)
- malignancies (eg rhabdomyosarcoma)
- skin tag

What is the DDX of a neonatal abdominal mass?

- 1) Kidney (65%)
 - **hydronephrosis (UPJO, UVJO, ureterocele, etc) } ~30%**
 - **MCDK } 25-35% (single most common entity)**
 - PCKD } 20%
 - renal vein thrombosis
 - solid tumour (eg Wilms' tumour, congenital mesoblastic nephroma)
 - ectopy
- 2) Retroperitoneum (10%)
 - **neuroblastoma } 17% (most common extra-cranial tumour in kids)**
 - teratoma
 - hemangioma
 - abscess
- 3) Bladder (1%)
 - PUV
 - female genital system
 - hydrocolpos
 - ovarian cyst
- 4) GI (12%)
 - duplication
 - giant cystic meconium ileus
 - mesenteric cyst
 - ileal atresia
 - ileal volvulus
 - gastric teratoma
 - colonic leiomyosarcoma
 - meconium peritonitis with ascites
 - ascites
- 5) Hepatobiliary (3%)
 - liver hemangioma
 - solitary liver cyst
 - hepatoma
 - distended GB
- 6) choledochal cyst
 - adenomatoid malformation of the lung

THE PEDIATRIC UROLOGY OFFICE VISIT

What is involved in the assessment of the ambulatory pediatric urology patient?

- 1) Observation and Hx
 - colour (pale or cyanotic), level of alertness, response to parent's comforting, quality of interaction with examiner, quantity of tears while crying
 - why is child here? What goals do the patient & family have?
 - direct hx toward child when possible
 - characterize pain or complaints (fever, abdo pain, scrotal pain, rectal pain, LUTS, etc)
 - characterize voiding symptoms (bowel & bladder), if any, and include eating & drinking pattern
 - PMHx, developmental milestones, meds, allergies, etc
- 2) physical exam
 - appearance } generalized edema (eg hypoproteinemia) vs localized edema of extremity (eg coarctation of aorta in Turner's baby)
 - } skin exam (café au lait spots, brittle nails, abN hair, etc)
 - } broadened epicanthal folds, hypertelorism, micrognathia, & low-set ears often assoc'd w/ congenital syndrome w/ a GU problem
 - } preauricular pits assoc'd with renal anomalies (bronchi-oto-renal dysplasia)
 - VS's } varies with age
 - } temp >41C associated with significant pathology (avoid ASA due to Reye's)
 - abdo exam } abdo muscle laxity (prune-belly syndrome, profound antenatal hydro), ventral hernias, umbilical drainage, masses
 - renal pathology accounts for up to 2/3 of neonatal abdo masses
 - lower back } look for any evidence of presacral dimpling or cutaneous markers of occult spinal dysraphism (eg dermal sinuses, human tails, Faun tail, etc)
 - "atypical" dimple (off centre >2.5cm or deeper than 0.5cm) may indicate spina bifida or cord tethering
 - external genital exam } inguinal canal, testes, scrotum, penis, vagina, perineum
 - block internal ring when examining inguinal canal to prevent migration of testis into abdomen
 - } **symmetrical gonadal exam suggests global d/o (eg CAH or AIS) vs asymmetrical gonadal exam which suggests localized problem (eg MGD or true hermaphroditism)**
 - } glanular adhesions to foreskin are N (shouldn't be separated)
 - if no UTI or balanitis, let prepuce separate naturally
 - usually occurs by age 4
 - } short ventral foreskin or curvature may indicate hypospadias or epispadias → **DO NOT PERFORM CX**
 - } imperforate hymen may result in hydrometrocolpos (lower abdo mass)
 - } adhesions of labia minora are normal
 - neuro exam } may be difficult in infants
 - } absent anal wink + patulous anus may indicate low spinal cord lesion
- 3) lab investigations
 - urinalysis & urine C&S } mode of obtaining specimen important
 - } pyuria is >5 WBCs/HPF (girls) or >3 WBCs/HPF (boys)
 - more confirmatory than diagnostic for UTI
 - } UTI is >100,000 cfu or if symptomatic then >10,000 cfu
 - WBC casts and urinary sediment suggest pyelo
 - } microscopic hematuria (>5 RBCs/HPF in 2/3 urinalyses) is common in kids w/ no cause found in most kids
 - } **gross hematuria more common in viral cystitis than acute bacterial cystitis**

4) imaging

- U/S } gives good anatomic info on KUB
 - can't distinguish obstructive from nonobstructive hydro w/o good hx and comparison studies
 - } also used to differentiate torsion from epididymitis and hernia from hydrocele
 - } **if <6months, U/S can be used to assess suspected occult spinal dysraphism**
 - ossification of posterior elements occurs after 6 months of age
 - especially accurate for low lying cord
- VCUG } gives info on VUR, PVR & anatomy of bladder & outlet during filling & voiding
 - } look at spine, ribs, pelvis on plain film as well as presence of stones
 - } use feeding tube not Foley (can obscure BN and trigone anatomy)
 - } should repeat filling & voiding so ectopic ureter & VUR is not missed
 - } VCUG modified to image urethra & vagina simultaneously in patients w/ UG sinus
- nuclear cystograms } 1st exam to screen of siblings of refluxers & also to reassess kids with known VUR
- renal scans } best for abN's in renal perfusion, secretion and filtration
 - } not as good as CT, MRI, U/S for morphologic abN's
 - } can measure cortical binding and tubular binding phases
- renal scintigraphy } can use gallium-67 or indium-111 labeled leukocytes
 - } can help diagnose and localize the site of UTIs
- IVP } inspect plain film for stones, spinal abN's, and abN gas patterns
 - } nephrogram phase can identify renal masses and renal scarring after pyelo
 - } good to assess GU tract anatomy
- CT } replaced IVP in most cases of suspected stones
 - } good to assess solid tumours
- MRI } may provide the best info
 - } UPJO, ectopic ureter draining into SV cyst, identification of impalpable testis
 - } requires sedation in most kids

What are the causes of failure to thrive (FTT)?

→ FTT is used to describe children whose physical growth is significantly less than that of his/her peers

→ **non-organic causes** (more common than organic causes in N America)

- poverty
- poor child-parent interaction
- child abuse
- maternal depression
- family discord

→ **organic causes**

→ organic causes of insufficient growth are:

- a) failure of parent to offer adequate calories
- b) failure of child to take sufficient calories
- c) failure of child to retain sufficient calories
- **renal } UTI, RTA, DI, CRF**
- GI } GERD, celiac disease, pyloric stenosis, cleft palate/lip, lactose intolerance, Hirschsprung's disease, milk protein intolerance, hepatitis, cirrhosis, pancreatic insufficiency, biliary disease, IBD, malabsorption
- cardiopulmonary } disease leading to CHF, asthma, bronchopulmonary dysplasia, CF, anatomic abNs of upper airway, obstructive sleep apnea
- endocrine } hypoT4, DM, adrenal insufficiency or excess, PTH disorders, pituitary disorders, GH deficiency
- neurologic } MR, cerebral hemorrhages, degenerative disorders
- infectious } parasitic or bacterial infections of GI tract, TB, HIV
- metabolic } inborn errors of metabolism
- congenital } chromosomal abNs, congenital syndromes (fetal EtOH syndrome), TORCH infections
- miscellaneous } lead poisoning, malignancy, collagen vascular disease, recurrent infected adenoids & tonsils

What is the approach to FTT based on age (CHART)?

→ birth to 3 months

- psychosocial FTT
- perinatal TORCH infections
- GERD
- inborn errors of metabolism
- CF

→ 3-6 months

- psychosocial FTT
- HIV
- GERD
- inborn errors of metabolism
- milk protein intolerance
- CF
- RTA

→ 7-12 months

- psychosocial FTT (autonomy struggles)
- delayed introduction of solids
- GERD
- intestinal parasites
- RTA

→ >12 months

- psychosocial FTT (coercive feeding, new psychological stressor)
- GERD

When should fevers be treated in children?

- same circadian rhythm as adults } usually 1C higher later in day
- temp <39C } treat only for comfort
 - } may be beneficial in high-risk kids with chronic lung disease, metabolic d/o's, or neurologic disease
- temp >41C } always need antipyretic therapy
 - } associated with severe infection, hypothalamic disorders, or CNS hemorrhage
 - } ASA not recommended due to risk of Reye's syndrome (liver and brain issues)
 - } acetaminophen (10-15mg/kg q4h) or ibuprofen (5-10 mg/kg q6h)

Which febrile patients are at increased risk of serious infections?

Table 110-8 -- Febrile Patients at Increased Risk for Serious Bacterial Infections

Condition	Comment
<i>Immunocompetent Patients</i>	
Neonates (<28 days)	Sepsis and meningitis caused by group B streptococci, <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , herpes simplex virus
Infants <3 mo	Serious bacterial disease (10–15%); bacteremia in 5% of febrile infants
Infants and children 3–36 mo	Occult bacteremia in 4%; increased risk with temperature >39°C and white blood cell count >15,000/μL
Hyperpyrexia (>41°C)	Meningitis, bacteremia, pneumonia, heatstroke, hemorrhagic shock–encephalopathy syndrome
Fever with petechiae	Bacteremia and meningitis caused by <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> type b, <i>Streptococcus pneumoniae</i>
<i>Immunocompromised Patients</i>	
Sickle cell anemia	Pneumococcal sepsis, meningitis
Asplenia	Encapsulated bacteria
Complement/properdin deficiency	Meningococcal sepsis
Agammaglobulinemia	Bacteremia, sinopulmonary infection
Acquired immunodeficiency syndrome	<i>S. pneumoniae</i> , <i>H. influenzae</i> type b, <i>Salmonella</i>
Congenital heart disease	Increased risk of endocarditis
Central venous line	<i>Staphylococcus aureus</i> , coagulase–negative staphylococci, <i>Candida</i>
Malignancy	Gram–negative enteric bacteria, <i>S. aureus</i> coagulase–negative staphylococci, <i>Candida</i>

From Powell KR: Fever. In Behrman R, Kliegman R, Jenson H (eds): *Nelson Textbook of Pediatrics*, 16th ed. Philadelphia, WB Saunders, 2000, p 74.

What are the findings associated with Beckwith-Wiedemann syndrome?

- macroglossia
- hepatosplenomegaly
- nephromegaly
- hypoglycemia from pancreatic beta cell hyperplasia
- gigantism
- Wilms' tumour
- adrenal carcinoma

What is the DDx of a CYSTIC abdominal mass in a kid?

- **hydronephrosis (most common)**
- **multicystic dysplastic kidneys (MCDK most common multicystic mass)**
- adrenal hemorrhage
- hydrometrocolpos
- intestinal duplication
- choledochal, ovarian, omental, or pancreatic cysts

List RFs associated with renal vein thrombosis in a child } } } “Premature SPUD CANT Dance”

- Prematurity
- Sepsis
- Polycythemia
- Umbilical artery catheterization
- Dehydration
- Coagulopathies (eg antithrombin-3 or protein C deficiencies)
- Asphyxia
- Nephrotic syndrome
- Trauma/Tumour
- DM mothers

What is the significance of café-au-lait spots?

- uniformly hyperpigmented sharply demarcated macular lesions } may vary in size
- can be present at birth or develop during childhood
- **normal to have 1-3 spots**
- if ≥ 5 café-au-lait spots each $> 5\text{mm}$ in prepubertal kids or if ≥ 6 spots $> 15\text{mm}$ in postpubertal kids then must r/o NF type 1 (von Recklinghausen's disease)

What is the significance of an omphalocele?

- omphalocele is a herniation of intra-abdominal contents **through the umbilicus WITH coverage by membrane**
 → gastroschisis is a herniation of intra-abdominal contents through the lateral abdo wall (normal umbilicus) **WITHOUT** membrane coverage
- omphaloceles are associated with other anomalies such as Beckwith-Wiedemann, Down's, myelomeningocele, imperforate anus

What is the management of a hydrocele in an infant?

- if true hydrocele and no changes in volume, processus vaginalis is usually not patent and so will resolve by 1yr
- if symptomatic, persistent after 12-18mos or changes in volume (communicating), surgery indicated

What are some physical symptoms suspicious for possible sexual abuse?

- vaginal, penile, or rectal pain, D/C, or bleeding
- chronic dysuria, enuresis, constipation, or encopresis
- documented STDs
- bruising of vaginal mucosa with dilated vaginal opening or damaged hymen (v-shaped notch or cleft)

What is the management of urethral prolapse?

- more common in pre-pubertal black F & post-menopausal F
- can present as a sensitive mass that bleeds with contact
- Rx → topical estrogen + expectant management if voiding normal
 → surgery if abN voiding or failed medical management

What are the developmental milestones of a normal child?

Table 110-10 -- Developmental Milestones

Age (mo)	Gross Motor	Fine Motor	Social Skills	Language
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with one hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of six blocks	Plays with others	2-3 word sentences

From Haslam RHA:Neurological examination. In Behrman R, Kliegman R, Jenson H (eds):Nelson Textbook of Pediatrics,16th ed. Philadelphia, Elsevier, 2000.

What are the different types of radionuclide renal scans?

- 1) DTPA } diethylenetriaminepentaacetic acid
 } almost 100% filtration
 → can estimate GFR
 } shouldn't be used in neonates
- 2) MAG-3 } mercaptoacetyl triglycine
 } ~100% secretion (some say ~20% filtration)
 } **can also estimate RPF**
- 3) DMSA } dimercaptosuccinic acid
 } 65% secretion + 35% filtration
 } good to identify renal scarring and for differential function

What pediatric outpatient procedures can be done in the office?

- UDS
- biofeedback training
- Cx for infants <3 months of age
 - GOMCO clamp, Plastibell, Mogen clamp
 - meta-analysis found dorsal penile nerve block more effective than EMLA
 - usually use both local + EMLA
- meatotomy \ liberal use of petroleum jelly
- lysis of labial adhesions / to prevent complications

What are the potential complications after neonatal Cx?

- minor
 - bleeding
 - wound infection
 - meatal stenosis
 - secondary phimosis (from insufficient removal of foreskin or inner preputial skin)
 - preputial-glanular bridge formation
- major
 - sepsis
 - amputation of distal glans
 - removal of excessive foreskin
 - urethrocutaneous fistula

What is the management of hematuria in a child?

- gross hematuria
 - Hx and P/E
 - VS's
 - labs } urinalysis, urine C&S, CBC, lytes, creatinine,
 - imaging } abdo U/S
 - } cysto rarely indicated
- microhematuria
 - Hx and P/E
 - VS's
 - labs } urinalysis, urine C&S, CBC, lytes, creatinine,
 - if large amount of proteinuria } refer to nephro
 - if small amount of proteinuria } repeat over 2-3 wks
 - imaging } abdo U/S
 - } cysto rarely indicated

What are the indications for the cystoscopy in a child?

→ diagnostic

- persistent gross hematuria with all other tests N
- bladder mass

→ therapeutic

- PUV ablation
- ureterocele

What is the DDx of a umbilical leakage in an infant?

- patent urachus
- external urachal sinus
- omphalitis
- simple granulation of healing stump
- patent vitelline/omphalomesenteric duct
- infected umbilical vessel

Chapter #111 – Renal Disease in Kids

HEMATURIA

What is the definition of hematuria?

→ **most common urinary abN'ity in kids that leads to referral to urologist/nephrologist**

- **≥5 RBCs per HPF** } must differentiate from pigmenturia (hemoglobinurina/myoglobinuria)
- gross vs microscopic
- asymptomatic vs symptomatic (LUTS or signs of glomerular disease)
- intermittent vs persistent
- found in ~1% of healthy kids

What are the common causes of hematuria in kids?

1) Glomerular (dysmorphic RBCs + RBC casts)

- **IgA nephropathy (Berger's disease)** → **most common glomerular cause (30%)**
- Glomerulonephritis
 - primary } nonproliferative (minimal change, membranous, FSGS)
 - } proliferative (post-infectious GN, RPGN/crescentic, diffuse proliferative, mesangial proliferative)
 - } crossover (membranoproliferative)
 - secondary } collagen vascular disease (SLE)
 - } vasculitis (Henoch Schonlein purpura)
 - } Goodpasture's
- sickle cell nephropathy
- **HUS** } **most common cause of ARF in kids**
- thin GBM disease
- familial nephritis (Alport's syndrome)
- infectious } SBE, Hep B associated GN

2) Non-glomerular (eumorphic RBCs + no casts)

- medical
 - **hypercalciuria** } **most common non-glomerular cause**
 - nephrocalcinosis
 - exercise
 - cystic kidney disease } PCKD, MSK
 - vascular disease } renal artery thrombosis, AVF, renal vein thrombosis
 - coagulopathy } DIC, hemophilia, thrombocytopenia
 - **UTIs (most common cause of isolated gross hematuria)**
- surgical
 - stones
 - trauma
 - tumour } RCC, TCC
 - GU tract anomalies } hydronephrosis, VUR, meatal stenosis, UPJO
 - perineal irritation (common – 10%)
 - meatal stenosis with ulceration
 - urethrorrhagia

What are the 4 main categories of hematuria in kids?

- 1) gross
- 2) microscopic + symptoms
- 3) **asymptomatic isolated microscopic** } **usually benign condition in kids**
- 4) asymptomatic + proteinuria } if proteinuria significant, will need Bx as likely glomerular dz

What are the causes of pseudohematuria?

- Heme +ve
 - hemoglobinuria (hemolysis, sepsis, dialysis)
 - myoglobinuria (DKA, myositis, trauma)
- Heme -ve
 - drugs (sulfa, nitrofurantoin, salicylates)
 - foods (beets, food colouring, etc)
 - metabolites (porphyria, etc)

What is the work-up for hematuria in kids?

- 1) Hx and P/E
 - LUTS
 - flank pain
 - constitutional symptoms
 - fever, rash, pallor, anemia
 - arthralgias
 - edema
 - HTN
 - abdo masses
- 2) Family Hx
 - stones
 - renal disease
- 3) Gross hematuria
 - a) lab tests } CBC, lytes, BUN, creatinine, urine R&M, urine C&S, urine Ca excretion
 - b) imaging } renal U/S→ if still no Dx, refer to pediatric nephrologists/urologist (consider cystoscopy)
- 4) Microscopic hematuria
 - if symptomatic, perform symptom-specific evaluation + renal U/S
 - if asymptomatic
 - a) lab tests } urine R&M
 - if isolated (no proteinuria) } repeat R&M x 2-3 times
 - if continued isolated micro refer to nephro + renal U/S
 - if + proteinuria } need to quantitate urine protein
 - } if $>4 \text{ mg/m}^2/\text{hr}$ or $\text{UPr/Cr} >0.2$
 - refer to nephro
 - } if $<4 \text{ mg/m}^2/\text{hr}$ or $\text{UPr/Cr} <0.2$
 - re-evaluate
 - refer to nephro if hematuria + proteinuria
 - b) imaging tests } renal U/S if persistent microscopic hematuria

What are the indications for the cystoscopy in a child?

- diagnostic
 - persistent gross hematuria w/ all other tests N
 - bladder mass
- therapeutic
 - PUV ablation
 - ureterocele

PROTEINURIA

What is the definition of proteinuria?

→ **2nd most common urinary abN'ty in kids that leads to referral to urologist/nephrologist**

- may be transient, may indicate inflammation, or glomerular disease
 - rarely can indicate tubular disease
- orthostatic proteinuria is benign (usually found in older kids)
 - no proteinuria in morning sample
- usually first detected on dipstick (albumin)
 - trace is ~15mg/dL → 3+ is ~300mg/dL
 - 1+ is ~30mg/dL → 4+ is ≥2000mg/dL
 - 2+ is ~100mg/dL
- asymptomatic, isolated proteinuria is common on screening urinalysis in kids

What are the potential causes for a FALSE –VE reading for PROTEINURIA on dipstick?

- acidic urine
- dilute urine
- primary protein not albumin } if urine –ve on dip but +ve w/ 3% sulfosalicylic acid, test for MM

What are the potential causes for a FALSE +VE reading for PROTEINURIA on dipstick?

- alkaline urine
- highly concentrated sample
- significant gross hematuria
- antiseptic cleanser
- contrast agents in urine

How is urinary protein excretion quantitated?

→ **most important diagnostic test**

→ N urine protein excretion in kids is <4mg/m²/hr (<100mg/m²/day)

→ 4-40mg/m²/hr is abN

→ >40 mg/m²/hr is Nephrotic range

- classic method } timed urine collection
 - need to measure urinary creatinine level to make sure adequate sample (15-20mg/kg/day for girls & 20-25mg/kg/day for boys)
- new methods } random urine protein:creatinine ratio
 - <0.5 is normal for kids 6months to 2yrs old
 - <0.2 is normal for kids >2yrs old

What is the work-up of proteinuria?

- 1) transient proteinuria } may be associated with fever, stress, dehydration, and exercise
 - repeat AM void urine dipstick in 1yr
- 2) orthostatic proteinuria } benign (should not be >1g/day)
 - no further work-up
- 3) persistent proteinuria } defined as ≥1+ proteinuria on dipstick on >1 occasion
 - Hx and P/E
 - LUTS
 - UTIs
 - HTN
 - edema
 - meds
 - incontinence
 - growth failure (ht, wt)
 - polyuria
 - presence of systemic disease
 - Family Hx
 - renal disease
 - Lab tests
 - repeat AM void urine R&M and do urine protein:creat ratio
 - if abN proceed w/ full w/u } abN urinalysis or UPr/Cr >0.2
 - CBC, lytes, creat, BUN, cholesterol, albumin
 - based on hx also consider } serum C3/C4, ANA, Hep B & C, HIV, anti-streptolysin O
 - Imaging
 - consider renal U/S
 - refer to nephrologists (renal Bx to be considered)

NEPHROLITHIASIS

How do stones present in kids?

- often depends on age
- hematuria } in ~30% of all age groups
- pain } more common with older ages ie 50% if >11yrs of age
- incidental finding on work-up for UTI or other reason } more common in younger kids

What are the most common types of stones in kids?

- ~75% **Ca stones** } **Ca oxalate most common**
- 13% struvite
- 5% cystine
- 4% uric acid
- 4% mixed/other

What are the common causes of stones in kids?

- 1) GU tract anomalies
- 2) hypercalciuria
- 3) idiopathic
- 4) infection

List causes of stones in neonates

→ ‘DUTTCH Stones in Really Little Suckers’

- Dehydration
- Underweight (low birth wt)
- Theophylline
- TPN
- Cystinuria
- HyperPTH’ism (congenital)
- Sepsis
- RTA
- Lasix
- Steroids

Calcium stones

What is the classification of Calcium stones?

- 1) Hypercalciuria (>4 mg/kg/day)
 - **underlying cause in ~1/3 of kids with stones**
 - often found on w/u of isolated hematuria } **hematuria + hypercalciuria is often a precursor of renal stones**
 - a) **primary idiopathic hypercalciuria (most common cause in kids)**
 - b) absorptive } type 1 and type 2
 - c) renal leak } distal RTA, Bartter’s, Dent’s, etc
 - d) resorptive } primary hyperPTH, etc
- 2) hypocitraturic Ca stones → distal RTA, chronic diarrheal, thiazide induced, idiopathic, ↑ purine diet
→ most commonly occurring combined abN’ity
- 3) hyperuricosuric Ca stones
 - accounts for ~8% of stones in kids
 - consider inborn errors of metabolism } gout is uncommon in kids
→ Lesch-Nyhan, glycogen storage disease type 1, myeloproliferative d/o, etc
- 4) hyperoxaluric Ca stones
 - accounts for ~3-11% of stones in kids
 - a) idiopathic
 - b) primary hyperoxaluria } type 1 and 2
 - c) enteric
 - d) dietary
- 5) hypomagnesiuric Ca stones → IBD + malabsorption

What are the causes of hypercalciuria?

- 1) absorptive hypercalciuria
 - increased Ca excretion after oral Ca load
 - **N fasting urinary Ca (most cases) + N serum Ca + N or suppressed PTH**
 - possibly related to Vit D receptor upregulation
 - type 1 } hypercalciuria despite low Ca diet (severe & less common)
 - type 2 } normal Ca excretion on restricted Ca diet
- 2) renal leak hypercalciuria
 - impaired PCT reabsorption of Ca
 - leads to secondary hyperPTH'ism
 - **↑ fasting urinary Ca + N serum Ca + ↑ PTH + ↑ Vit D**
 - possibly related to Na intake, PGs, genetic abnormalities (Dent's, Bartter's)
- 3) resorptive hypercalciuria (uncommon)
 - **usually associated with primary hyperPTH'ism**
 - **↑ urinary Ca + hyperCa + ↑ PTH + ↑ Vit D**
 - high PTH results in ↑'d gut absorption (Vit D) & ↑'d bone resorption
 - hyperCa present in most cases, BUT can rarely be N
 - then resembles renal leak if N serum Ca
 - if truly resorptive, serum Ca will worsen after "thiazide challenge"
 - also get elevated urinary PO₄ and cAMP levels found
 - can also be due to malignancy (↑ PTH), sarcoid (↑ Vit D), TB, hyperT₄, pho, etc
- 4) **primary idiopathic hypercalciuria } most common cause of hypercalciuria, which is the most common cause of Ca stones in kids**

What is the management of primary idiopathic hypercalciuria in kids?

- 1) diet } increased fluid intake
 - } Na restriction
 - } increase in dietary K
- 2) medications } HCTZ (if clinically significant stone disease)
 - } K citrate

What are the causes of hypocitraturia?

- 1) distal RTA
 - inability to acidify urine after oral acid load (NH₄Cl)
 - high urine pH (>6.8), high serum chloride, hypoK and low serum HCO₃ (met acidosis)
- 2) diarrheal states
 - intestinal alkali loss results in systemic acidosis
- 3) thiazide-induced
 - induce hypoK and intracellular acidosis
- 4) high-protein diet
 - acid load
- 5) idiopathic

What are the causes of hyperuricosuria?

- at higher risk of uric acid stone & Ca oxalate stones
 - stone formers with hyperuricosuria have higher rates of stone formation and more severe symptoms
- 1) dietary excess of purines
 - 2) uric acid overproduction } Lesch-Nyhan, myeloproliferative & lymphoproliferative d/o's, multiple myeloma, hemoglobinopathies & thalassemia, ketogenic diet for sz's

What are the causes of hyperoxaluria?

- 1) idiopathic
- 2) primary oxalosis
 - rare **AR disorder** that prevents conversion of glyoxylate to glycine
 - glyoxalate gets converted in liver to oxalate instead } **get >100mg/day of oxalate**
 - aggressive stone formation, nephrocalcinosis
 - type 1 = **lack of AGT** enzyme (liver)
 - type 2 = lack of glyoxylate reductase (liver) } less aggressive course wrt renal failure
 - if un-Rx'd (liver-kidney Tx), 50% will have ESRD by age 15 and is assoc'd with ~30% death rate
 - Rx → high fluid intake
 - Na/K citrate (stone inhibitors)
 - use of diuretics
 - trial of pyroxidine
 - need liver-kidney Tx
- 3) enteric (most common acquired cause)
 - chronic diarrheal states (Crohn's, Celiac sprue, short gut, small bowel resection, etc)
 - fat malabsorption results in saponification of FA's with Ca & Mg
 - results in **↑'d oxalate available for absorption** d.t. ↓'d Ca/Mg complexing
 - malabsorbed FA's & bile salts cause **↑'d oxalate absorption in colon too**
 - also get **dehydration, hypoK, hypomagnesuria, hypocitraturia, acidic urine**
- 4) dietary
 - ↑'d oxalate-rich diet (nuts, chocolate, spinach, broccoli, strawberries, rhubarb, brewed tea)
 - ↑'d Vit C diet
 - may be due to **absence of *Oxalobacter formigenes*** (oxalate-degrading bacterium)

What are the 3 main phenotypes of primary hyperoxaluria type 1?

- 1) severe infantile } systemic oxalate deposition + renal failure
- 2) adult-onset } occasional stones
- 3) childhood presentation } most common phenotype
 - } nephrocalcinosis + stones + progressive renal insufficiency

What are the causes of hypomagnesuria?

- rare cause of Ca stones
 - Mg complexes with oxalate and Ca
 - associated with low citrate levels
- 1) poor dietary intake
 - 2) reduced intestinal absorption } diarrheal states (IBD, etc)

Cystine Stones

What is the cause of cystine stones?

- represents ~5% of renal stones in kids
- **defect in PCT** that results in failure to reabsorb COLA amino acids

What are the 3 main inheritance patterns of cystinuria?

- 1) **type 1 } most common (70%)**
 - } AR mutation of SLC3A1 gene on chromosome 2p
 - } early stone formers
- 2) type 2 \ various combinations all resulting in mutations
- 3) type 3 / of SLC7A9 gene on chromosome 19

What is the management of cystine stones?

- 1) diet } increased fluid intake
- 2) meds } cystine chelators (penicillamine-D, alpha-MPG/thiola, captopril, Bucillamine)
 - } urine alkalinization (K citrate, Mucomyst, Acetazolamide)

Struvite stones

What are the causes of struvite stones in kids?

- GU tract anomalies
- obstruction

Other

What are some other causes of stones in kids?

- chemo for leukemia
- ceftriaxone
- kidney transplant

Evaluation and Management

What is the initial work-up of a child with stones?

- 1) Hx and P/E
 - symptoms
 - growth
 - include dietary and family hx
- 2) Lab tests
 - urinalysis
 - 24hr urine collection
 - urine creatinine, Ca, oxalate, uric acid, citrate, cystine, pH, total volume, Na, K, Mg

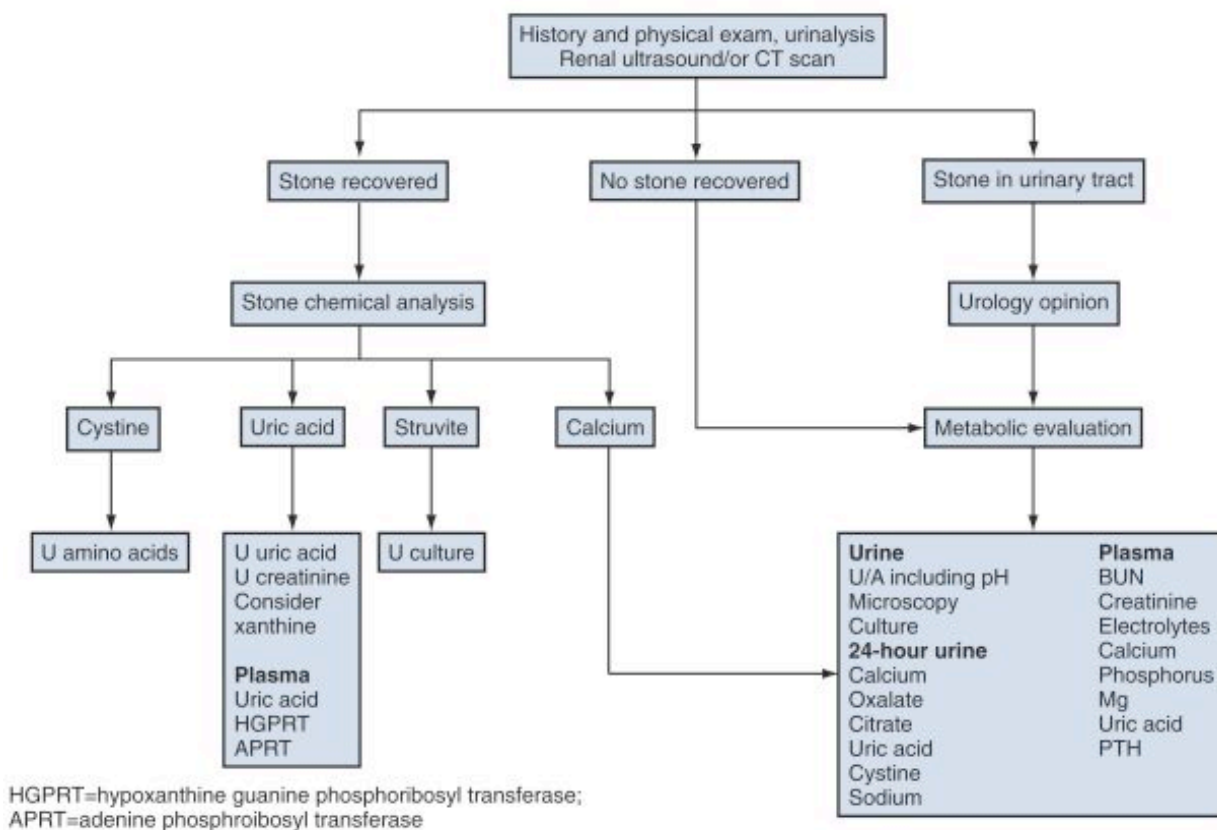
Table 111-2 -- Normal Urinary Values for School-Aged Children

Calcium	<4 mg/kg/day (or alternative-random urine Ca/Cr <0.21)
Uric acid	<0.56 mg/dL glomerular filtration rate [(urine uric acid/urine creatinine)/plasma creatinine]
Oxalate	<50 mg/1.73 m ² /day
Citrate	>300 mg/g creatinine
Cystine	<60 mg/1.73 m ² /day
Creatinine	15-25 mg/kg/day (higher for males compared to females)
Volume	>20 mL/kg/day

What is the algorithm recommended in the evaluation of stones in kids?

- 1) Hx and P/E
 - should include family hx and dietary hx
 - note growth
- 2) Lab tests
 - CBC, lytes, BUN, creatinine, Ca, PO₄, Mg, uric acid, PTH
 - urinalysis, urine C&S
 - 24hr urine collection for creatinine, total volume, Ca, oxalate, uric acid, citrate, cystine, pH, Na, K, Mg
 - done while kid is infection free and on routine diet
- 3) imaging
 - renal U/S
 - renal CT
- 4) stone analysis
 - when available

***** AGGRESSIVE METABOLIC EVALUATION AND TREATMENT IS WARRANTED IN KIDS WITH STONES OR NEPHROCALCINOSIS *****



RENAL PARENCHYMAL DISEASES COMMON IN KIDS

What is important in a nephro Hx and P/E for a child?

→ Hx

- fatigue, malaise
- abdo pain, N/V
- family hx
- prior streptococcal illness (think GN)
- viral illness + hematuria (think IgA nephropathy)
- meds history

→ P/E

- BP, ht, wt, small stature
- flank pain, abdo tenderness, renal enlargement, masses, rashes
- edema (think nephrotic syndromes)
- chest for fluid overload

What is nephrotic syndrome?

→ **edema + hypoalbuminemia + hyperlipidemia + heavy proteinuria**

- heavy proteinuria } $>40\text{mg}/\text{m}^2/\text{hr}$ or a random urine protein:creatinine ratio >3.0
- hypoalbuminemia } $\leq 2.5\text{g}/\text{dL}$
- disease of the **glomerular podocyte**
- primary (eg minimal change disease, FSGS) VS secondary (membranous - SLE) VS congenital
- kids usually present with edema (+/- ascites, genital edema, etc)

What are the main causes of NEPHROTIC syndrome in kids?

- 1) minimal change disease } **most common cause of primary nephrotic syndrome in kids**
 } aka “**steroid-responsive**” nephrotic syndrome
 → majority respond well to steroids
 } more common in younger kids (≤ 10 yrs)
 } presents w/ edema, appears well, and has N renal function & BP
 } fatty casts & oval fat bodies
- 2) FSGS } 2nd most common cause of primary nephrotic syndrome in kids
 } **more common in older kids & in black kids**
 } less likely to respond to steroids
 → only 20-25% respond
 } doesn't always have all 4 features of nephrotic syndrome
 → eg may present with isolated proteinuria
 } leads to ESRD if heavy proteinuria persists
 } **recurs in ~50% of patients even after renal Tx**
- 3) membranous } thickened glomerular BM from immune deposits
 } primary or secondary (SLE, hepatitis B, congenital syphilis, etc)
 → **less common cause of nephrotic syndrome of adults (5% vs 30%)**
 → **more likely to be secondary in kids**
 } microscopic hematuria common but HTN rare
 } ~20% progress to ESRD, ~40% have remission
- 4) membranoproliferative
- 5) mesangial proliferative

What is congenital nephrotic syndrome?

- **onset of symptoms before or shortly after birth**
 → **hypoalbuminemia + hyperlipidemia + proteinuria + hypogammaglobulinemia**
 - several subtypes, but **Finnish subtype is most common (AR inheritance)**
 → premature birth + large placental weight
 → mutation in NPHS1 gene with absence of nephrin protein
 - may also have other causes:
 → diffuse mesangial sclerosis
 → Denys-Drash syndrome } male pseudohermaphroditism + Wilms' tumour + glomerulopathy
- Rx → aggressive replacement of albumin + immunoglobulins
 → nutritional support
 → early unilateral or bilateral Nx + dialysis & renal Tx

What complications are associated with nephrotic syndrome?

- 1) increased risk of infections (loss of urinary opsonins) } high risk of spontaneous bacterial peritonitis
- 2) hypercoagulable state (loss of protein C&S, etc) } avoid central venous catheters
- 3) ESRD

What is the initial management of presumed nephrotic syndrome?

- 1) dietary NaCl restriction
- 2) oral steroids } recommended even if likelihood of response low (eg FSGS)
 } prednisone 60 mg/m²/day x 4wks, then 40mg/m²/day q2days x 4wks, then taper off
 → most kids respond with remission of proteinuria within 4 weeks
 → 2/3 of kids will have a relapse
 } iv methylprednisone may be better
 → better for younger, non-Blacks
- 3) other immunosuppressants } cyclophosphamide or cyclosporine
 } indicated if frequent relapses or unable to taper off steroids w/o relapse
- 4) renoprotective agents } ACE inhibitors or ARBs
- 5) lipid-lowering agents
- 6) renal Bx } if older kid (>10 yrs old) or if no response to steroids

What is nephritic syndrome?

- **gross hematuria + HTN + ESRD at presentation + immune activation (low C3)**
+ **mild proteinuria + RBC casts**
- involves all 3 cellular components of glomerulus } **endothelial & mesangial cells** are 1° site of injury
- focal (IgA, Henoch-Schonlein purpura, etc) VS diffuse (MPGN, RPGN, etc)

What are the main causes of NEPHRITIC syndrome in kids?

- 1) post-infectious GN } usually occurs **after group A strept infections (eg pharyngitis)**
 - latency period of ~7-21 days
 - } **most common cause of acute GN in kids**
 - } usually presents with edema + cola-coloured urine + HTN
 - } Dx made with **+ve antistreptolysin-O + decreased serum C3**
 - } acute phase (2wks) can range from oliguric renal dysfxn to anuria needing IHD
 - } complete renal recovery in >90%
 - micro hematuria and proteinuria may persist for 3-12 months
 - hypoC3 usually resolves within 2 months
 - Rx → supportive management
- 2) IgA nephropathy } **often presents with gross hematuria associated w/ URTI**
(Berger's)
 - gross hematuria usually resolves after respiratory infection
 - } **more common in older kids**
 - Dx made on renal Bx (mesangial proliferation + IgA deposits)
 - } progression to ESRD is not uncommon (15% after 10yrs and 30-50% after 20yrs)
 - } ~50% will have remission at some point
 - Rx → ACE inhibitors
 - steroids +/- MMF
- 3) Henoch-Schonlein } **often presents w/ palpable purpuric rash + abdo pain + refusal to wt bear**
Purpura } considered an acute GN (arthralgia)
 - } **more common in younger kids (considered a vasculitis)**
 - } may develop IgA and ~50% develop ESRD in 10yrs
 - Rx → ACE inhibitors
 - immunosuppressive agents if more aggressive
- 4) SLE nephritis } **presents w/ proteinuria + micro hematuria + HTN + mild renal insufficiency**
 - } commonly presents with fever, arthralgia, rash, Coombs' +ve anemia
 - 80% female and renal involvement more common in kids with SLE (80%)
 - } can also cause membranous GN (nephrotic syndrome in 50%)
 - } 5 different classifications
 - class IV (diffuse proliferative) is most common (~40%)
 - } often see decreased C3/C4 during acute illness
 - Rx → steroids + cytotoxic therapy (cyclophosphamide or MMF)
 - ACE inhibitors
- 5) HUS } **hemolytic microangiopathic anemia + thrombocytopenia + renal insufficiency**
 - **most common cause of ARF in kids** (HTN, fluid overload, oligoanuria)
 - } typical form (associated with diarrhea due to enterotoxigenic *E. coli*)
 - 70% of kids with typical form present with prodrome of **bloody diarrhea**
 - HUS symptoms present 4-7 days after diarrhea
 - renal involvement associated to severity of GI prodrome
 - } atypical form (not associated diarrhea) may be due to:
 - Strept-associated HUS
 - complement factor H deficiency
 - abN vWF protease inhibitor
 - abN vit B12 metabolism
 - post-BMTx
 - calcineurin inhibitor-associated HUS
 - } neurologic involvement occurs in 20% (seizures, encephalopathy, or coma)
 - } irreversible renal failure seen in ~5%
 - Rx → supportive } fluids & electrolytes (watch out for hyperK)
 - } transfusions for anemia (no platelet transfusions)
 - } dialysis as needed
 - no ABx for enterocolitis

What are the poor prognostic factors associated HUS?

- nondiarrheal, atypical form
- <1yr old
- prolonged anuria
- severe HTN
- severe CNS disease

What renal functional abnormalities are seen in pts w/ sickle cell?

- increased total RBF
- decreased flow in vasa recta
- decreased maximum urine osmolality in response to water deprivation
- abN lowering of urine pH in response to acid loading
- increased tubular secretion of uric acid

What are the features of sickle-cell nephropathy?

- hematuria (dysmorphic RBCs) } M > F
 - papillary necrosis
 - glomerulopathy
 - nephrogenic DI
 - incomplete RTA
 - hyperuricemia
 - asymptomatic bacteriuria
- Rx → bed rest, hydration, oxygen
→ alkalization, aminocaproic acid, IV diuresis

List GU manifestations of sickle cell disease/trait. (AUA Update #18 – '05)

→ **HUGE F'N PRIAPISM**

- Hematuria (dysmorphic RBCs) } M > F and L side 4x more than R
- UTIs
- Glomerular disease (MPGN, immune complex GN, etc) } leads to proteinuria
- ED
- Frequency, polyuria, etc (Nephrogenic DI)
- Nocturnal enuresis
- Priapism
- RTA (distal)
- Infertility
- ARF
- Papillary necrosis
- Infarcts (renal medulla, testicular)
- Slow (chronic) renal failure
- Medullary RCC (trait)

What is Alport's syndrome?

- consists of **hereditary nephritis + high-frequency hearing loss + ocular abN'ities**
 - X-linked in >80% } 15% AR and <5% AD
- family hx of deafness & ARF
- leads to ARF in 2nd to 3rd decade of life

RENAL TUBULAR DISORDERS

What are the different types of renal tubular disorders?

- congenital VS acquired
- proximal (eg Fanconi's syndrome) VS distal (eg distal RTA, Bartter's, Gitelman's)

Proximal Tubule Disorders

What are the main functions of the proximal tubule?

- **reabsorption of bulk of filtrate** } mainly depends on favorable Na gradient created by the Na-K-ATPase pump
- water
- Na
- K
- HCO₃
- glucose
- phosphate
- amino acids
- uric acid
- small molecular wt proteins
- **most electrolytes, proteins are reabsorbed in PCT** } **only exception is Mg**
(65% thick ascending limb of loop)

What are the most common proximal tubule disorders?

- 1) disorders that interfere w/ energy production by PCT } results in generalized dysfunction
→ ie Fanconi syndrome
- 2) isolated transport disorders of PCT } much less common
→ eg proximal RTA (type 2)

What is Fanconi's syndrome?

- **not a specific disorder but the combination of tubular loss of numerous substrates**
- inherited VS acquired
- usually present with **polyuria + signs of dehydration + symptoms of electrolyte depletion**
 - rickets } **hypoPO₄** and calcitriol deficiency
 - muscle weakness } **hypoK**
 - growth failure } **metabolic acidosis**
 - constipation } dehydration
 - hypouricemia } common in kids
- more likely to be inborn error of metabolism the younger the kid
- Rx → electrolyte replacement (eg K citrate, Na Phosphate, etc)
 - Vit D
 - indomethacin (reduces urinary losses)
 - treatment specific to cause (eg cysteamine for cystinosis)

What are the causes of Fanconi's syndrome (CHART)?

- inborn errors of metabolism
 - **cystinosis (most common)**
 - galactosemia
 - hereditary fructose intolerance
 - tyrosinemia
 - Wilson's disease
 - glycogen storage disease (type 1)
 - cytochrome C deficiency
 - Lowe's syndrome
- intoxications
 - heavy metals (lead, cadmium)
 - glue sniffing
- meds
 - gentamicin
 - ifosfamide
- other
 - multiple myeloma
 - Sjogren's syndrome

Distal Tubule Disorders

What are some of the most common distal tubule disorders?

1) Distal RTA (type 1 RTA)

- usually presents in infancy with **polyuria + vomiting + dehydration + FTT + hypoK + non-anion gap metabolic ACIDOSIS**
- mutation in H⁺ - ATPase pump found in CCD
 - **can't acidify urine** (no H⁺ excretion), even after acid challenge
- acquired VS congenital
 - AD inheritance (less severe form) or AR inheritance (more severe, infantile form)
 - more severe AR form usually accompanied w/ hearing loss + nephrocalcinosis and may progress to renal insufficiency
- characterized by **hypercalciuria + hypocitraturia**
 - explains high prevalence of nephrocalcinosis and renal stones (CaPO₄)

Rx → NaHCO₃ or K citrate supplementation (base)

→ need ~2-3 mEq/kg/day } even more req'd for proximal RTA

2) Bartter's syndrome

- group of transport disorders with variable degrees of clinical expression
 - **primary defect is K & Cl loss**
- usually presents with **hypoK + metabolic ALKALOSIS + polyuria + growth failure + salt craving + constipation (dehydration) + hypoCl**
- classic Bartter's syndrome
 - hypomagnesemia + hypercalciuria } can lead to nephrocalcinosis
- neonatal Bartter's syndrome
 - most severe form with severe polyuria } may have polyhydramnios
 - get severe hypercalciuria + early nephrocalcinosis

Rx → KCl supplementation (5 mEq/kg/day)

→ +/- prostaglandin synthetase inhibitors (indomethacin) to reduce urinary losses

3) Gitelman's syndrome

- similar to Bartter's syndrome but presents later in life with less severe systemic effects
- usually presents with **muscle weakness or tetany +/- abdo pain, vomiting & fever**
- **HYPOcalciuria differentiates from Bartter's syndrome**

Rx → Mg repletion +/- occasionally KCl supplementation needed

What are the 3 types of Bartter's syndrome?

- Type 1 (neonatal Bartter's)
 - "congenital Lasix"
 - defects at gene coding for renal Na-K-2CL cotransporter and ROMK channel
- Type 2 (classic Bartter's)
 - deletion/mutation for renal Cl channel gene
- Type 3 (Gitelman's syndrome)
 - "congenital HCTZ"
 - defect in gene for thiazide-sensitive NaCl cotransporter

NEPHROGENIC DIABETES INSIPIDUS

What is nephrogenic DI?

- characterized by **polyuria + excessive thirst + hyperNa + inability to concentrate urine**
 - due to a defect in the renal tubular response to vasopressin/ADH
 - **X-linked recessive mutation** of ADH receptor is most common form
 - less common form involves mutation in aquaporin-2 water channel
 - most cases diagnosed in 1st yr of life
 - usually presents with vomiting, anorexia, FTT, fever, constipation, polydipsia, and developmental delay
 - Dx made with **dilute urine (Urine Osm <300) in presence of hypernatremic dehydration**
 - high urine output can result in **severe hydro, urinary retention, nocturnal enuresis, or transient ureteric dilation**
- Rx → HCTZ + amiloride } decreases urine output, increases urine [] and conserves K
→ Ringer's Lactate if dehydrated

What are the causes of nephrogenic DI?

→ "OLD CARP FISH"

- | | | |
|----------------|-----------------------|-------------------------|
| - Obstruction | - Ca excess (hyperCa) | - Familial (primary XR) |
| - Lithium | - AmphoB/Amyloidosis | - Idiopathic |
| - Demeocycline | - Renal failure | - Sick cell |
| | - PCKD | - HypoK |
- primary form is **x-linked recessive mutation (more common)**
- homozygous defect in AQP2 channel

CARE OF THE CHILD WITH CRF AND ESRD

What is the classification of chronic renal failure in kids?

- | | |
|-----------------------|--|
| - stage 1 } GFR ≥90 | } adult classification system now used for kids also |
| - stage 2 } GFR 60-89 | |
| - stage 3 } GFR 30-59 | |
| - stage 4 } GFR 15-29 | |
| - stage 5 } GFR <15 | |

How is GFR estimated in kids (CHART)?

→ Schwartz formula

- | | | |
|--------------------------------|---|---|
| 1) age <18months | } | $\frac{\text{Ht (cm)} \times \mathbf{0.45}}{\text{creatinine (mg/dL)}}$ |
| 2) age >18 months and wt <70kg | } | $\frac{\text{Ht (cm)} \times \mathbf{0.55}}{\text{creatinine (mg/dL)}}$ |
| 3) male with wt >70kg | } | $\frac{\text{Ht (cm)} \times \mathbf{0.70}}{\text{creatinine (mg/dL)}}$ |

What are the common causes of renal failure in kids (CHART)?

- 1) **obstructive nephropathy (23%)**
- 2) hypoplasia/dysplasia (18%)
- 3) chronic GN (10%)
- 4) VUR (9%)
- 5) FSGS (8%)
- 6) PCKD (4%)
- 7) Eagle-Barrett (3%)
- 8) HUS (2%) → most common cause of ARF in kids
- 9) Cystinosis (1.5%)
- 10) Wilms' tumour (<1%)
- 11) DM (<1%)

What are the principles in caring for kids with chronic renal failure?

- 1) renoprotective efforts to slow progression
→ HTN, hypercholesterolemia } ACEi, ARBs, lipid-lowering agents
- 2) correction of associated metabolic disturbances
→ hyperPTH (from PO₄ retention, low calcitriol synthesis) } calcitriol + low PO₄ diet
 } PO₄ binders

→ metabolic acidosis } NaHCO₃
→ anemia } iron +/- Epo
- 3) provision of nutritional & hormonal support for growth failure
→ consider supplemental tube feeds (G-tube)
→ consider recombinant HGH injections
- 4) preparation for renal replacement therapy (preferably Tx)
→ consider RRT once CrCl is ≤25 mL/min/1.73m²
→ assess bladder function
→ consider need for pre-Tx nephrectomy
→ give needed immunizations
→ consider potential living donors } make sure kid is big enough (>15kg)
 } if kidney is large and child small, can't perfuse graft well so RISK OF GRAFT THROMBOSIS

What are the indications for initiating dialysis in kids with CRF?

- symptomatic uremia
- inability to maintain metabolic control with meds
- renal clearance $< 10 \text{ mL/min/1.73m}^2$

Chapter #112 – Infections & Inflammation of the Pediatric GU Tract

EPIDEMIOLOGY OF PEDIATRIC UTI'S

How common are UTIs in kids?

- UTI accounts for ~1% of all pediatric office visits
- more common in M during first year of life } 10x more common if uncircumcised male (1% vs 0.1%)
- more common in F once >6-12months of age (1-3% vs <1%) } even more common in sexually active F
- younger infants 3x more likely to be hospitalized for UTI than older kids
→ girls hospitalized 2.5x more often for UTI than boys

What are the factors that suggest complicated UTI? }} “ACADEMIC WHIP”

- AbN or anomalous GU tract } calyceal diverticulum, bladder diverticulum, neurogenic bladder, etc
- **Children**
- ABx use (recent)
- **DM**
- **Elderly**
- **Male**
- Immunosuppression
- Catheterized
- Week-long symptoms at presentation (7days)
- Hospital-acquired
- Instrumentation (recent)
- Pregnancy

How are pediatric UTIs categorized (CHART)?

- | | |
|--------------------|----------------------------------|
| 1) first infection | 2) recurrent or other infections |
| a) symptomatic | a) unresolved |
| b) asymptomatic | b) persistent |
| | c) reinfection |

What are the causes of unresolved bacteriuria?

- 1) **bacterial resistance to ABx (most common)**
- 2) development of resistance from initially susceptible bacteria → occurs in 5%
- 3) bacteriuria caused by 2 bacterial species with mutually exclusive susceptibilities
- 4) rapid infection with a new, resistant species during original therapy
- 5) renal failure (urine concentration too low)
- 6) non-compliance

List causes of surgically correctable bacterial persistence in children (CHART)

→ “PUFFED UP MASK”

- | | |
|---------------------------|---|
| - Papillary necrosis | - Urachal cyst (infected) |
| - Ureteral stump | - Prostatitis (chronic) |
| - FB | - MSK |
| - Fistulae | - Abscess (perivesical, perinephric) |
| - Ectopic ureter | - Stones (infected) } most common cause |
| - Diverticulum (urethral) | - Kidney (atrophic segment) |

What bacterial virulence factors exist that increase the likelihood of UTIs? }}} “Hokus-POKEUS”

- **Hemolysin & mannose-resistant Hemagglutination (MRHA)**
- **Pili or fimbriae (type 1 pili, P pili, P fimbriae)**
- **O antigen (cell wall)**
- **K antigen (cell wall)**
- **Exotoxin production**
- **Urease production**
- **Siderophore production**

What host/urinary defence factors inhibit bacterial growth? }} “LOCAL Grown STUUF”

- Lactobacillus
- Organic acids
- Cytokines & PMNs
- Acidic urine pH
- Lactoferrin
- Glucose low in urine
- Salts
- Tamm-Horsfall proteins
- Urea
- Umbrella cell shedding
- Flow of dilute urine (voiding) } most important

What are the most common bacterial organisms causing pediatric UTIs?

- Gran negatives } *E. coli* (most common), *Proteus*, *Klebsiella*, etc
- Gram positives } *Enterococcus faecalis*

PATHOGENESIS OF UTI'S IN KIDS

What is the natural course of UTIs in kids?

- 3% of girls get pre-pubertal UTI
 - 1% of boys get pre-pubertal UTI
- \ 17% develop infection-related renal scarring
 / → of these, 10-20% get HTN
 → but, progression to ESRD is rare

What are the urethral defenses that protect against retrograde ascent of periurethral bacteria?

- 1) urethral washout
- 2) epithelial shedding
- 3) paraurethral glandular secretion

What are the RFs for UTI (CHART)?

- age } more common at extremes of life – neonates & elderly
- gender } more common in boys during 1st yr of life, otherwise more common in girls
- race & ethnicity } less common in blacks
- blood group antigens on urothelium } P1 blood group, Le (a-b-), Le (a+b-), etc
- family hx } mother with UTI, sister with UTI, etc
- renal scarring } scarred kidneys beget more scarring from infection
- colonization } periurethral, preputial, fecal
- native immunity } IgG and IgA is lowest during first few months of life
 } longer breast feeding associated with lower risk of UTIs
- sexual activity
- GU tract abnormalities } VUR
 } pregnancy (risk of bacteriuria same, but higher rate of pyelo)
 } neurogenic bladder (higher risk of renal damage also)
 → no benefit w/ prophylactic Abx or sterile catheters
- iatrogenic factors } GU tract is most common site of nosocomial infection

What are the potential effects of UTIs during pregnancy on the fetus?

- mental retardation or developmental delay
- fetal death
- low birth weight
- **prematurity (pre-term labour) } common**

How well do symptoms correlate with localization of bacteria (cystitis vs pyelonephritis)?

- <50% of symptomatic kids (fever, flank pain) had upper tract bacteria
- 20% of asymptomatic kids had upper tract bacteria

DIAGNOSIS OF UTI

What is the prevalence of UTI in febrile kids?

- depends on age and sex
- risk of renal scarring makes prompt Dx and treatment essential
- **5-15% in infants <1yr } mostly males**

How does a UTI present in kids?

- infants & young children
 - **fever (70%)**
 - irritability (55%)
 - poor feeding (40%)
 - older children
 - dysuria
 - S/P pain
 - voiding dysfunction
 - adolescents
 - dysuria
 - frequency
 - urgency
- vomiting (35%)
 - diarrhea (35%)
 - abdo distension (8%)
 - jaundice (7%)
 - incontinence
 - flank or abdo pain
 - may still present with vague symptoms
 - hematuria
 - UTI in teen may be marker of sexual activity

What features have been found to be predictive of UTI as the source of fever in girls?

- **presence of 2 of 5 suggest urine culture should be done**
- 1) <12 months old
 - 2) white
 - 3) absence of other fever source
 - 4) temp >39C
 - 5) fever of ≥2days

What are the sequelae of STDs in teenage girls?

- must always r/o STD in girls suspected of UTI } prevalence of *Chlamydia* is 13-26%
- } prevalence of *N. gonorrhoeae* is 2-10%
- PID (10-40%)
- infertility (12%)
- chronic pelvic pain

What is the most reliable way to obtain a good urinary specimen?

- 1) suprapubic aspirate \ **only acceptable methods in**
- 2) catheterization (discard 1st portion) / **non-toilet trained kids**
- 3) MSU void
→ not reliable in young girls & young uncircumcised boys
- 4) “bagged” specimen (usually contaminated – better as test to r/o UTI when negative)
→ unacceptable in infants and high-risk population

What features on urinalysis are used to Dx a UTI in kids?

- gold standard for Dx is urine C&S
- 1) pyuria } >5 WBCs per HPF
 - 2) **microscopic evidence of any bacteria on HPF } overall most sensitive & specific**
 - 3) leukocyte esterase
 - 4) nitrites (very high specificity also)

What serum markers have been associated with UTI severity?

- 1) C-reactive protein (CRP) >7 mg/dL } **fever + elevated CRP + VUR increases risk of**
- 2) elevated procalcitonin **renal damage by 10-fold**
- 3) IL-6

How do you diagnose a UTI in a child (CHART)?

Method	Colony count	Probability of infection
S/P aspiration	any # of GNB	>99%
	>few thousand GPC	>99%
urethral catheterization	>10⁶	95%
clean void		
→ boy	>10⁴	infection likely
→ girl	3 specimens ≥10⁶	95%
	2 specimens ≥10⁶	90%
	1 specimens ≥10⁶	80%
	5 x 10 ⁴ to 10 ⁶	suspicious, repeat
	<10 ⁴	infection unlikely

How does pyelonephritis usually present in kids?

- fever
- chills
- unilateral or bilateral flank pain +/- LUTS (dysuria, frequency, urgency)
- non-specific abdo discomfort
- cloudy and malodorous urine
- urinalysis } WBCs, WBC casts, RBCs, bacteria

What are the physiologic changes seen in the GU tract with a bacterial infection?

- ureteral stasis
- elevated renal pelvic pressures
- renal inflammatory changes

What are the imaging features of pyelonephritis?

- renal enlargement } focal enlargement suggests acute lobar nephronia or focal bacterial pyelo
- areas of decreased perfusion in kidney
- impaired or delayed excretion
- dilation of collecting system with thickening of renal pelvis
- perinephric stranding

How does pyonephrosis present in kids?

- accumulation of purulent debris & sediment in the renal pelvis and collecting system
- similar clinical symptoms as pyelonephritis + obstructive hydronephrosis
- most obstructed pyonephrotic kidneys are non-functioning or poorly functioning
- imaging } shifting fluid-debris levels w/ changes in position, persistent echoes from lower collecting system, air in collecting system, weak echoes (pus) in dilated poorly transonic renal collecting system

Rx → ABx

→ prompt drainage

→ eventual evaluation of obstruction & renal function once acute infection treated

How do perinephric or renal abscesses present in kids?

→ uncommon in kids } now most common organism is *Proteus* & ***E. coli*** (used to be *S. Aureus*)

- fever
- flank pain
- leukocytosis
- sepsis

Rx → Abx +/- percutaneous drainage (required in most)

MANAGEMENT OF PEDIATRIC UTI'S

What are the 3 main goals of managing pediatric UTIs?

- 1) minimize renal damage during acute infection } key is rapid Dx and early treatment
- 2) minimize risk of future renal damage from subsequent UTIs
- 3) decrease risk of antimicrobial resistance

What are the guidelines for VCUG in children following a UTI?

- 1) any child with febrile UTI
- 2) any boy with UTI
- 3) any child with UTI ≤5yrs old (debatable in real clinical settings)

Why are UTIs in infants <3 months of age treated differently?

- 1) decreased immune system
 - 2) UTIs account for 2/3 of serious bacterial infection
 - 3) asymptomatic jaundice (especially if onset >1wk from birth) may represent UTI
- consider Listeria & GBS (perinatal infection) if UTI in child <30days

What are the indications for iv ABx in kids with UTIs?

- 1) systemically ill kids <2-3 months old
- 2) fever + flank pain (pyelo)
- 3) unable to take fluids
- 4) immunocompromised

What are the common ABx used in kids with UTIs (CHART)?

- urosepsis or <3mos old } 3rd GEN cephalosporin (ceftriaxone, ceftazidime, etc) +/- aminoglycoside
 - } Pip-Tazo
 - } Imipenem or Meropenem
 - } ampicillin +/- aminoglycoside
- acute uncomplicated pyelonephritis } fluoroquinolone
 - } amoxicillin/clavulanate
 - } 3rd generation cephalosporin
- acute uncomplicated UTI } TMP-SMX } cephalosporin (keflex, cefuroxime)
 - } penicillins (amoxicillin) } azithromycin
 - } fluoroquinolone } nitrofurantoin

What are the general principles of treating febrile UTIs in kids?

- iv broad spectrum ABx until afebrile } 90% afebrile by 48hrs
- change to specific po ABx once urine C&S returns } limit Abx use to shortest effective duration & narrowest spectrum
- continue po ABx for 10days
- **no f/u C&S needed after 48hrs if organisms sensitive to ABx used**
- once course of ABx finished, start prophylaxis until full radiologic evaluation of GU tract
- prophylactic agent is ideally not same as treating agent

What is the recommended management of uncomplicated UTIs in older children?

- 7-10 day course of oral broad-spectrum ABx
- in kids, longer course is better than 3-5 day course } more likely to have GU tract abN'ity

Which Abx have increased resistance patterns?

- TMP-SMX } 30% of *E. coli*
- ampicillin
- cipro
- resistance rates to nitrofurantoin have not changed

What are the RFs of developing a drug-resistant UTIs?

- 1) DM
- 2) recent hospitalization
- 3) recent use of ABx (especially TMP-SMX → 30% resistance)
- 4) ABx prophylaxis
- 5) GU tract anomalies (eg VUR, spina bifida, etc)
- 6) urethral catheters
- 7) younger age
- 8) prior UTI
- 9) recent travel outside US

PROPHYLACTIC ANTIMICROBIAL AGENTS

What are the indications for GU tract ABx prophylaxis in kids (CHART)?

→ **"Before 2-3 months, VIPs Prescribe Abx In Reflux"**

- 1) first UTI **before 2-3 months of age**
 - 2) VUR
 - 3) Instrumentation (urethral)
 - 4) Partial GU tract obstruction eg UPJO, ureterocele
 - 5) Prenatal hydronephrosis (prior to work-up)
 - 6) Awaiting radiologic evaluation after acute febrile UTI
 - 7) Immunosuppressed or immunocompromised
 - 8) Recurrent UTIs + normal GU tract
- ?CIC in child with VUR

What are the features of the ideal prophylactic ABx agent?

- low serum []
- high urinary []
- easily administered & tolerated
- cost-effective
- minimal effect on N fecal flora

What are the common Abx agents used for prophylaxis in kids (CHART)?

→ useful & tested

- nitrofurantoin } contraindicated in G6PD deficiency & if <1 month of age
 } long-term Rx associated with pulmonary fibrosis
 } 1-2 mg/kg
 S/E's → GI upset, peripheral neuropathy, pneumonitis, liver toxicity
- TMP-SMX } contraindicated if <2 months of age (kernicterus)
 } high resistance rates have developed
 } TMP diffuses into vaginal fluid & decreases vaginal colonization
 } based on 2 mg/kg of TMP
 S/E's → rash, GI upset, photosensitivity, Stevens-Johnson syndrome,
 hepatotoxicity, leukopenia
- keflex } 2-3 mg/kg
 S/E's → anaphylaxis, C diff, neutropenia

→ possibly useful

- amoxicillin
- TMP
- sulfisoxazole

→ NB } therapeutic agent should NOT be same as prophylactic agent

→ fecal flora already resistant to treating drug

→ period of greatest risk of recurrent UTI is first few wks after full-dose Rx

List factors associated with TMP-SMX resistance (CHART).

- 1) Abx use for >4wks during last 6 mos (OR = 23.4)
- 2) ≥ 2 hospital admission in last 1 yr (OR = 3.2)
- 3) GU tract abnormality (OR = 2.4)
- 4) 1 hospital admission in last 1 yr (OR = 2.3)
- 5) age between 2 and 6yrs (OR = 1)

List the main advantages & disadvantages of using nitrofurantoin as UTI prophylaxis.

- advantages } minimal resistance
- } covers most pathogens
- } minimal effect on fecal flora
- } high urine concentration

- disadvantages } ineffective against *Proteus* & *Pseudomonas*
- } poorly tolerated
- } contraindicated if <1 month old
- } contraindicated in G6PD deficient patients
- } contraindicated in renal failure
- } poor tissue penetration

IMAGING EVALUATION

What is the role of imaging in pediatric UTIs?

- 1) evaluate & localize acute urinary infection
- 2) detect renal damage from acute infection
- 3) identify GU anatomy that increases risk of future renal damage from infection
- 4) evaluate change in GU tract over time

What imaging studies are used in the evaluation of a pediatric UTI?

- 1) abdo U/S
- 2) VCUG
 - ?nuclear VCUG if re-evaluation or screening of sibling
- 3) +/- DMSA renal scan
 - evidence of VUR
 - ?at time of 1st UTI

What are some indications for EARLY IMAGING of the GU tract?

→ **after Rx of initial UTI, all kids should be on prophylactic Abx until radiologic evaluation**

→ seriously ill or febrile child with ("UP UP Away")

- Unclear source of infection
- Poor response to Abx after 2-3 days
- Unusual organism (eg TB, Proteus)
- Partial obstruction (known) } UPJO, ureterocele, megaureter, papillary necrosis, neurogenic bladder, poorly functioning kidney or poorly functioning kidney, etc
- Azotemia (new Dx)

What are some limitations of early imaging for UTIs?

- 1) overestimation of renal size } initial edema
- 2) underestimation of renal scarring } mature scars can take up to 2yrs to be seen

What is the recommended f/u imaging after initial radiologic work-up?

- 1) no abN'ity found
→ no routine studies
- 2) N collecting system but evidence of renal damage (generalized or focal edema, area of hypoperfusion)
→ f/u imaging recommended (look for scarring or shrinkage)
- 3) previously N studies (U/S and VCUG) but recurrent symptomatic pyelonephritis
→ nuclear VCUG may be more sensitive

SPECIFIC IMAGING TECHNIQUES

When should the VCUG be performed?

- can be done as soon as urine is sterile & voiding is normal
→ UTI likely does not cause VUR so there is no reason to wait 3-6 wks
→ all kids should be on prophylactic ABx from time of UTI treatment until VCUG

What are the advantages of fluoroscopic VCUG & nuclear VCUG?

→ VCUG is essential in the evaluation of pediatric UTIs

- 1) fluoro VCUG } gives anatomic detail of urethra & bladder
 } better at defining degree of VUR
 → for evaluation of all initial UTIs
- 2) nuclear VCUG } more sensitive at detecting VUR
 } less radiation
 → **should not be used to evaluate 1st UTI**
 → mainly reserved for periodic f/u imaging or for screening of siblings

What are the advantages & disadvantages of renal U/S?

→ advantages

- non-invasive
- detects structural abN'ities (eg hydronephrosis, etc)
- can detect perinephritic collections

→ disadvantages

- **not as sensitive as DMSA at detecting subtle changes of acute UTI**
- operator dependent
- poor at detecting VUR
- not as good at detecting renal scarring (newer high-resolution U/S is almost as good)

What are the U/S findings during an acute infection?

- pyelonephritis } enlarged swollen kidneys
 } thickening of renal pelvis + ureteral dilatation
 } focal or diffuse hyperechogenicity
 } areas of hypoperfusion on Doppler
- focal pyelonephritis } focal enlargement
 } focal area of hypoperfusion on Doppler

What are the findings of UTI on DMSA?

- acutely } uptake defects (focal or generalized)
 } renal swelling
- after acute infection } normal pattern
 } generally diminished uptake + small kidneys
 } diminished uptake in medial kidney
 } diminished uptake in renal poles + polar defects

What are the advantages of the different renal scan used?

- **DTPA** } ~100% filtration >> **“glomerular tracer”**
 → good to measure GFR and obstruction
 } 20% extraction coefficient in mature kidney
 → **not as good when kidney function is low or immature**
- **MAG3** } ~100% tubular secretion (in PCT) >> **“tubular tracer”** (some say 20% filtration)
 → better image quality, more accurate numerical values } obstruction & GFR
 } higher extraction fraction (50% in mature kidney) with little cortical retention
 → **more accurate when kidney function is poor or immature**
 } can assess RPF also
- **DMSA** } 65% secretion + 35% filtration >> **“cortical tracer”**
 → **good for assessing parenchyma (scars) & split function**
 → gives information on GFR **but not good for UPJO (+ cortical retention)**

What are the advantages & disadvantages of IVP over DMSA?

- advantages } more detailed info of collecting system
 } especially good for calyces
- disadvantages } more radiation
 } less sensitive at detecting scars
 } contrast

What are the 4 phases of renal enhancement on CT?

- 1) unenhanced phase (10-15 sec)
- 2) corticomedullary phase (~30 sec)
- 3) nephrographic phase (45 sec to 2min)
- 4) excretory phase (2-3min)

What are the findings of UTI on CT?

- renal enlargement (focal or diffuse)
- cortical hypoattenuation
- wedge defects
- poor corticomedullary differentiation
- linear bands of alternating hyper- and hypoattenuation (parallel to collecting ducts)
- perinephric stranding

SEQUELAE OF UTI

What factors affect renal scarring after UTI in kids?

- 17% develop infection-related renal scars
- pediatric kidney at greater risk for scarring from bacterial pyelo than mature kidney
- scarring requires VUR or intrarenal reflux + bacteriuria or high pressures
- 1) intra-renal reflux (poles are most common site of scarring – compound papillae)
- 2) pressure in GU tract (eg Pdet)
- 3) host immunity
- 4) age
- 5) timing of treatment
- 6) severity of VUR
- 7) # of UTIs (may be most important)

What are proposed methods to prevent the development of renal scarring associated with UTIs?

- early ABx treatment } delayed Rx associated with more scarring
- NSAIDs } may decrease scarring

What are the long term sequelae of renal scarring from VUR?

- HTN
 - occurs in 10-20% of kids with gross scarring } independent of degree of scarring
 - } possibly related to RAAS
- renal insufficiency
 - decrease in GFR correlates inversely with original degree of VUR
 - tubular dysfunction occurs early
 - can develop FSGS in future, even if renal function is relatively preserved
- proteinuria
 - progressive proteinuria common } can be significant (>1g per 24hrs)

How does XGP present in kids?

- rare in kids } infection + obstruction (stone or GU anomaly)
- **presentation is different than adults** } more common in boys (vs females)
- } more often focal (vs diffuse)

- flank pain
- fever & chills
- chronic bacteriuria (most commonly *Proteus* & *E. coli*)
- pyuria + proteinuria on urinalysis
- anemia
- malaise, malnutrition, weight loss, and FTT
- **foamy macrophages (xanthoma cells)**

- Rx → partial Nx for focal XGP
- complete Nx for diffuse XGP
 - ABx alone will rarely be adequate for focal XGP

What is the DDx of pediatric XGP?

- pediatric XGP can be confused w/ other childhood renal tumours
- Wilms'
- multilocular cystic nephroma
- congenital mesoblastic nephroma
- malignant rhabdoid
- clear cell sarcoma

MANAGEMENT OF SPECIAL UTI'S & COMMON ASSOCIATED PROBLEMS

How common is pyelonephritic scarring in the setting of VUR?

- 20-60% of kids investigated for UTIs have VUR
- 60% with renal scarring have VUR
- **risk of scarring increases with grade of reflux**

How common are recurrent UTIs?

- **recurrent UTIs overall more common in females, at any age**
- boys
 - <1yr old } 20% (rare to have infections more than 1 yr after initial UTI)
 - older boys } 30%
- girls
 - <1yr old } 25% (rare to have infections more than 1 yr after initial UTI)
 - older girls } 40%

What are the management options for recurrent UTIs associated with N GU tract?

- observation + UTI-associated ABx therapy (3-5days)
- prophylactic ABx regime

What is the correlation between VOIDING DYSFUNCTION and UTIs in kids?

- monosymptomatic nocturnal enuresis is NOT associated with UTIs
 - presence of diurnal enuresis IS associated with UTIs
- new diurnal enuresis develops in ~20% of kids that have recurrent UTIs
- UDS abnormalities common in kids with recurrent UTIs
 - symptoms may improve with sterile urine
 - treatment of persistent incontinence (eg anticholinergics) may decrease UTIs
- voiding dysfunction more common if kid is older than 3yrs of age at time of first UTI
- **must r/o tethered cord with new onset bladder dysfunction**

What is the correlation between CONSTIPATION and UTIs in kids?

- constipation more common in kids with UTIs
 - treatment of constipation may decrease incidence of UTIs
- **must r/o tethered cord with new onset bowel dysfunction**

What is the significance of asymptomatic UTIs in kids?

- most have history of voiding dysfunction, LUTS, or UTI on careful history
- **50% have normal GU tract**
- most develop persistent infections or reinfections
 - **should be evaluated just like any other UTI**
- renal scarring occurs independent of ABx therapy
 - presence of scars at initial evaluation is most predictive of future scarring
- **MAJORITY OF ASYMPTOMATIC BACTERIURIA with N GU TRACTS CLEAR WITHOUT ANY TREATMENT**

OTHER GU TRACT INFECTIONS & SYNDROMES

What is the most common cause of acute hemorrhagic cystitis in kids?

→ **60% have no infectious etiology**

- *E. coli* is most common bacterial cause (~17%)
- adenovirus is most common viral cause (~15%) } common after BM Tx & other states of immunosuppression
 - BK virus
 - adenovirus 11

What is the significance of pediatric epididymitis?

- bimodal age distribution } very young boys & post-pubertal men
- **presents as acute scrotum and testicular torsion must be ruled out } almost as common**
- epididymitis more likely with hx of gradual onset, dysuria, urethral D/C, recent GU tract Sx, recent urethral instrumentation, neurogenic bladder, imperforate anus, etc
- pyuria & bacteriuria is also highly suggestive of epididymitis
- cf to older males, epididymitis in kids more likely to be related to **GU tract anomalies or systemic hematogenous dissemination**
 - systemic spread can be due to *H. influenza B* (otitis media)
 - **think STDs in post-pubertal sexually active boys**

What is the management of pediatric epididymitis?

- r/o torsion
- broad-spectrum ABx
- analgesics and NSAIDs
- **radiologic evaluation of GU tract (as with any UTI) } renal U/S + VCUG**

What is the significance of TB epididymitis?

- most common form of GU TB
- can present as painless mass (r/o testis Ca) or painful scrotal swelling (r/o epididymo-orchitis)

What are the RFs for funguria in kids?

- ABx therapy
- prematurity
- intravenous or umbilical artery catheterization
- TPN
- immunocompromised status
- prophylactic oral nystatin or fluconazole in very low birth weight babies may prevent colonization & invasive fungal infections

What is the most common organism responsible for fungal infections in kids?

→ **kidney is most commonly involved organ** } fungal bezoars can cause obstruction

- 1) *Candida albicans* (~50%)
- 2) *Candida glabrata* (resistant to fluconazole)

What is the management of funguria?

- if assoc'd w/ indwelling catheter, Rx is recommended only if symptomatic or if >10K – 15K cfu/mL
- antifungal therapy } oral
 - } intravenous (fluconazole not approved for kids <6mos)
 - } intravesical amphotericin B
- change or remove all indwelling catheters
- urinary alkalization
- percutaneous NTs } +/- local irrigation
 - } +/- streptokinase if obstructing fungal bezoar that doesn't dissolve w/ meds
- surgical removal of any refractory obstructing fungal balls

GU TRACT & NOSOCOMIAL INFECTIONS

What are the CDC guidelines on wound infections?

→ not specific for kids & no GU operations were included

- 1) don't remove hair unless it interferes with surgery, and if removed, clip immediately pre-op
- 2) identify and treat all remote infections
- 3) early discharge from hospital
- 4) give ABx only as per recommendations
- 5) give ABx intravenously 60 minutes pre-op and continue coverage for few hrs post-op
- 6) bowel prep (mechanical & antimicrobial)
- 7) avoid routine vancomycin use

What are the 2 main RFs for nosocomial UTI in kids?

→ usually asymptomatic

- 1) urethral instrumentation
- 2) chronic indwelling catheterization

What are the recommendations for indwelling catheter care?

- 1) genital washing OD or BID with water & soap
- 2) regular emptying of collection bag
- 3) prophylactic ABx only recommended if at risk for endocarditis or if neutropenic
- 4) asymptomatic bacteriuria should only be Rx'd before GU tract manipulations or when drainage tube is removed (if catheter in for >4days, urine is considered infected)

What are some infectious complications of UTIs?

- bacteremia
- epididymitis-orchitis
- pyelonephritis
- periurethral abscesses
- struvite stones

BACTERIOLOGIC ECOLOGY & ANTIMICROBIAL RESISTANCE

What are the RFs of developing a drug-resistant UTIs?

- 1) DM
- 2) recent hospitalization
- 3) recent use of ABx (especially TMP-SMX → 30% resistance)
- 4) GU tract anomalies (eg VUR, spina bifida, etc)
- 5) urethral catheters
- 6) ABx prophylaxis
- 7) younger age
- 8) prior UTI
- 9) recent travel outside US

What are methods to decrease drug-resistant organism UTIs?

- 1) optimal use of ABx
- 2) restriction of classes or specific agents
- 3) rotational or cyclic usage of ABx
- 4) use of combination ABx therapy to decrease resistance

CONSIDERATIONS IN TREATING KIDS WITH UTI

What is involved in the evaluation of pediatric UTIs?

- 1) History
 - Present symptoms } **fever**
 - } details of UTI (onset, duration, Rx & investigations to date)
 - consider method of urine culture (bag, MSU, CIC, aspirate)
 - } LUTS, previous UTIs
 - } vague, non-localizing in infants (irritability, poor feeding, vomiting, etc)
 - } localized symptoms in older kids (S/P pain, back pain, dysuria, etc)
 - consider pyelo if fever, chills, flank pain, LUTS, etc
 - Voiding hx } toilet habits & baseline voiding symptoms
 - } constipation, previous UTIs
 - } tendency to curtsy or strain to void
 - } enuresis
 - **FmHx** } VUR in siblings, UTIs in family members, GU anomalies
 - PMHx } neurologic disease (spina bifida, etc.), circumcision, surgeries, syndromes
 - } meds, allergies
 - } prenatal hx (any antenatal U/S abnormality), developmental milestones
 - RFs for UTI } age, sexual activity, scarring, colonization, immune status, genetics (sex, race, virulence), GU abnormalities, iatrogenic
- 2) Physical exam
 - BP & growth chart plot
 - abdomen } masses, CVA tenderness, SP tenderness, palpable bladder
 - external genitalia } Boys (meatal stenosis, UDT, hypospadias, urethral D/C, epididymitis/orchitis, torsion)
 - } Girls (labial adhesions, interlabial mass (prolapse, ureterocele), ectopic ureteral opening, urethral discharge, vaginal abnormalities)
 - neurologic } hairy patch, sacral fat pads, gluteal cleft, sacral dimples/pits, anal wink
- 3) Urine
 - determine technique of urine retrieval } ensure true UTI (CIC or aspirated urine)
 - U/A } 4 determinations that support UTI
 - } +ve WBC + nitrites w/ microscopic bacteria on R&M = 100% sensitivity for UTI, or 100% NPV if all -ve
 - R&M } identification of bacteria in urine equivalent to > 30000 bacteria/mL
 - urine C&S } 95% probability if colony counts > 10^5 on CIC/voided urine
 - } 10^4 CFU/mL may still indicate significant UTI in clean voided in M
 - } **any number of bacteria on SP aspirate is significant**
- 4) Imaging
 - US } kidney, ureter, bladder, urethra, other abnormalities
 - } overall growth & development
 - VCUG } VUR, diverticula, urethra
 - DMSA if U/S or VCUG abN } early renal cortical lesions from pyelo can be seen w/ DMSA
 - 50-86% of w/ febrile UTI have renal scars on DMSA
 - 50% of these persist 2y later
 - CT } lobar nephronia visible
 - } for defining renal abnormalities when other modalities do not
 - UDS if evidence of neurologic dysfunction
- 5) Workup for pt presenting w/ UTI
 - **no f/u C&S needed after 48hrs if organisms sensitive to ABx used**
 - continue on prophylaxis until work-up complete

What is the management of pediatric UTIs?

- dependent on findings of investigations (PUV, VUR, duplication, nothing)
- 1st febrile UTI } abdo US + VCUG (DMSA if abnormal)
 - } maintain child on prophylaxis until studies complete
 - } surveillance, periodic VCUG/US
- recurrent UTI } nuclear VCUG more sensitive for VUR detection, but less anatomic detail
- screen siblings } US + VCUG if < 5yrs, US if > 5yrs
 - nuclear VCUG may be more appropriate than VCUG for screening sibs

Chapter #113 – Anomalies of the Upper Urinary Tract

How can one classify renal and ureteral anomalies?

- 1) anomalies of NUMBER
 - ageneis } bilateral (Potter's syndrome)
 } unilateral
 - supernumerary
- 2) anomalies of ASCENT
 - simple ectopia
 - cephalad ectopia
 - thoracic ectopia
- 3) anomalies of FORM and FUSION
 - crossed ectopia w/ fusion } unilateral fused kidney (inferior ectopia)
 } sigmoid or S-shaped kidney
 } lump kidney
 } L-shaped kidney
 } disc kidney
 } unilateral fused kidney (superior ectopia)
 - crossed ectopia w/o fusion } crossed ectopia without fusion
 } solitary crossed renal ectopia
 } bilaterally crossed renal ectopia
 - horseshoe kidney (most common fusion anomaly)
- 4) anomalies of VOLUME AND STRUCTURE
 - hypoplasia
 - multicystic kidney
 - polycystic } infantile vs adult (ARPKD vs ADPKD)
 - other cystic diseases
 - medullary cystic disease
- 5) anomalies of ROTATION
 - incomplete, excessive, or reverse
- 6) anomalies of RENAL VASCULATURE
 - aberrant, accessory, or multiple vessels
 - renal artery aneurysm
 - renal AV fistula
- 7) anomalies of the COLLECTING SYSTEM
 - calyx/infundibulum } calyceal diverticulum
 } hydrocalyx
 } megacalycosis
 } unipapillary kidney
 } extrarenal calyces
 } pseudotumour of kidney
 } infundibulopelvic stenosis
 - pelvis } extrarenal pelvis
 } bifid pelvis

ANOMALIES OF NUMBER

Agenesis

What is involved in the development of a normal kidney?

- intermediate mesoderm → pronephros → mesonephros → metanephros (adult kidney)
- **ureteric bud** sprouts from distal end of mesonephric duct (4th wk) and comes in contact with condensing **metanephric mesenchymal blastema**, inducing into the metanephric blastema
→ occurs between 5th and 7th week of gestation
- ureteric bud and metanephros travel up together
- **kidney reaches adult location by 8th or 9th week of gestation**

What causes renal agenesis?

- multifactorial
 - absence of nephrogenic ridge on dorsolateral aspect of the coelomic cavity
 - failure of a ureteral bud to develop from the mesonephric duct
- **need normal metanephric blastema AND ureteral bud for N kidney developments**
- likely a problem that prevents ureteral bud induction into metanephric blastema
 - if ureteric bud doesn't plug into metanephric blastema ... kidney tissue doesn't form

What is the epidemiology of bilateral renal agenesis (BRA)?

- aka Potter's syndrome
- rare, only ~**500 cases in literature**
- **M predominance (75%)**
- 40% of are stillborn & most others die w/in 48 hrs (respiratory distress from pulmonary hypoplasia)

What is the cause of Potter's syndrome?

- upper urinary tract anomaly with most profound effect on person
- no unifying cause → ?genetic cause with subsequent molecular basis
- adrenals not affected → different embryology
→ usually normally positioned
- no identifiable major renal artery

What are the RFs for Potter's syndrome?

- 1) increased maternal age → neither maternal disease nor complications of pregnancy influence development of BRA
- 2) family hx → genetic predisposition (~1000 fold increase)

What is the cause of pulmonary hypoplasia in Potter's babies?

- not sure but not just a compression factor
- oligohydramnios subsequent compression of chest wall
- lack of molecular signals → ?proline

What syndromes are associated with Potter's syndrome?

- 1) Frazer's syndrome → cryptophthalmos, orofacial defects, GU malformations, ↓'d # of digits
- 2) Klinefelter's syndrome → 47 XXY with hypogonadism, decreased mental ability
- 3) Kallmann's syndrome → congenital disorder of hypothalamic and pituitary function
→ get hypogonadisma and anosmia
- 4) esophageal atresia

List the common features of Potter's syndrome.

- low birth weight
- **oligohydramnios**
- IUGR
- **Potter's facies** → prominent skin fold around the eyes (key feature)
 - blunted nose
 - prominent depression between lower lip & chin
 - low-set broad & flat ears
- large claw-like hands
- bowed & clubbed legs with excessive hip flexion } can also get fused legs (sirenomelia)
- dry, loose skin
- **bell-shaped chest with pulmonary hypoplasia** (not just from mechanical compression)
- normal adrenals → but often flattened
- complete ureteral atresia seen in >50%
- **bladder present in only ~50%** → hypoplastic even if present
- poorly formed trigone → from failure of mesonephric duct structures incorporating into bladder base
- **UDT in ~40%**
- **genital anomalies** → more common in F, through rare to see Potter's in females overall
 - hypoplastic or absent ovaries
 - rudimentary, bicornuate or absent uterus
 - blind-ending or absent vagina
- lumbar meningocele
- **CV & GI abnormalities seen in up to 50%**

What is the epidemiology of UNILATERAL RENAL AGENESIS (URA)?

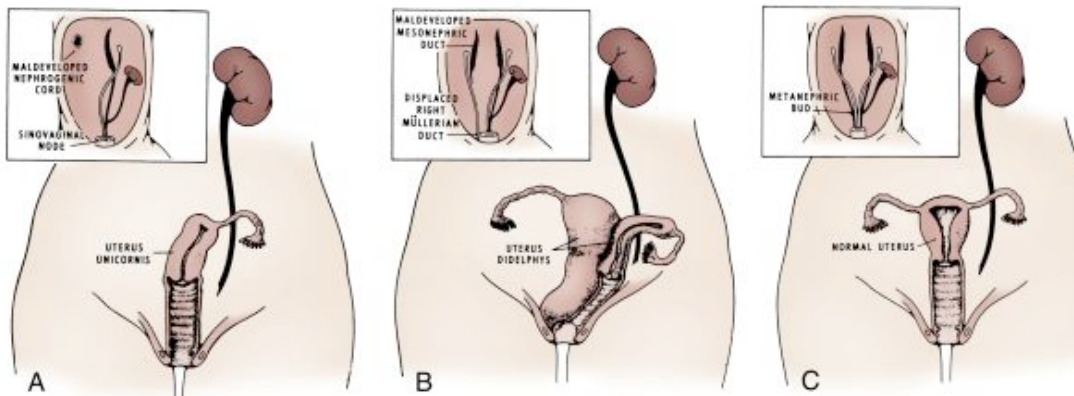
- ~1 in 1000 births
- **more common in M, but less so than Potter's syndrome → 1.8:1**
- more frequent on **L side**
- familial tendency → AD inheritance with variable penetrance (?chromosome 8, 22, X)

What is the cause of URA?

- similar to Potter's but unilateral
- either problem with nephrogenic ridge or with ureteral bud induction → probably ureteral bud

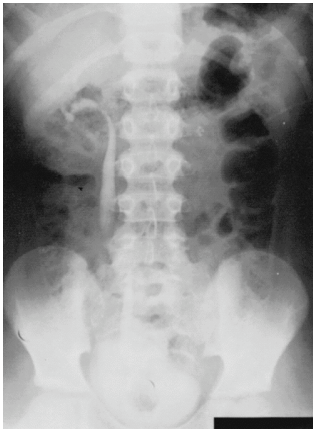
What are the embryological classifications of URA?

- 1) type I → insult before week 4
→ complete unilateral agenesis of GU structures (solitary kidney + **unicornuate uterus**)
- 2) type II → insult in week 4
→ **didelphys uterus** with obstruction of ipsilateral horn and vagina
- 3) type III → insult after week 4
→ **normal genital structures**



How do you differentiate URA from an involuted dysplastic or multicystic kidney?

- if splenic flexure is in N position, likely not URA } medial location of colon is likely URA



→ UNILATERAL RENAL AGENESIS

- absent L kidney + medial location splenic flexure

List the common features of URA?

- very rarely see ipsilateral adrenal agenesis (<10%) → often flattened
- abN ipsilateral ureter (never N) } completely absent in >50%
- hemitrigone or asymmetrical trigone
- anomalies of contralateral kidney rare } except for contralateral ectopia & malrotation
- contralateral ureteric anomalies common } **VUR (30%), UPJO (11%), UVJO (7%)**
- genital anomalies → again more common in F (25-50% vs 10-15% in males)
 - women → abN uterus, absent or abN vagina
(eg unilateral hematocolpos in pubertal girl)
 - men → absent epididymal tail, vas, SV, ejaculator duct, etc
(Wolffian structures)
- **CV anomalies (30%), GI anomalies (25%), and MSK anomalies (14%)**

Name anatomic findings suggestive of URA?

- females } abN internal genitalia (eg unicornuate uterus – MOST COMMON IN F)
 - } Gartner's duct cyst
- males } unilateral absence of vas (BAVD less common)
 - } absent body & tail of epididymis
 - } cystic dysplasia of rete testis
 - } SV anomalies (eg SV cyst)
 - } diphallia
 - } ectopic scrotum
- general } supernumerary nipples
 - } preauricular pits/tags
 - } congenital ear disorder with hearing loss

What syndromes are associated with URA? } } } “Frazer overTurned Bus on DVP, Killed Many”

- 1) **Frazer's syndrome** → cryptophthalmos, orofacial defects, GU malformations, ↓d # of digits
- 2) **Turner's syndrome** → 45, XO with underdeveloped genitals
- 3) **BOR syndrome** → brachio-oto-renal
- 4) **DiGeorge syndrome** → abnormal thymus, parathyroid, and great vessels (monosomy 22)
- 5) **VACTERL** → 20-30% have URA (vertebral, anal atresia, cardiac, TE fistula, renal, limb anomalies)
- 6) **Poland's syndrome** → ipsilateral abnormality of chest wall, upper limbs
- 7) **Kallmann's syndrome** → congenital disorder of hypothalamic and pituitary function
 - get hypogonadism and anosmia
- 8) **Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome**

Is the remaining kidney in URA patients at any increased risk of disease?

- NO } if really involuted MCDK, then risk of VUR (most common) & UPJO in other kidney
- Argueso et al, '92 } HTN (47%), proteinuria (19%), mild renal insufficiency (13%)
→ no long term survival difference

What is the management of URA?

- 1) consider VCUG } need to r/o VUR (30%)
- 2) counseling regarding solitary kidney

What is the recommendation for sports and activity?

- no restrictions } MVA is most common way to injure (we don't tell them not to drive)
- if playing sports wear protection (sledding, skiing, rollerblading, etc) } be aware of condition

What are the CUAJ guidelines on solitary kidney?

→ Psooy CUAJ 2009

- 1) outline to family that child has only 1 kidney and loss will result in need for dialysis or renal Tx
- 2) renal injury (of any etiology) increases risk of renal insufficiency
- 3) certain activities are higher risk for renal injury BUT risk of head injury is 5x higher in those activities
 - bicycling, sledding, downhill skiing, snowboarding, horse-back riding
 - snowboarding may be worse than downhill skiing
- 4) parents should keep things in perspective; if they wouldn't restrict activity based on child having only one head, they shouldn't restrict child based on having only one kidney
- 5) wearing protective padding during contact sports may decrease the risk of renal injury
- 6) renal injuries are much more common after MVAs, so wear seatbelt, bicycle protection, etc

Supernumerary kidney

What is a supernumerary kidney?

- accessory organ with its **own collecting system, blood supply & distinct parenchyma**
- either completely separate or only loosely attached to the major kidney on the ipsilateral side

What is the epidemiology of supernumerary kidneys?

- very rare } **~100 cases reported**
- more **common on L side**
- equal between M & F
- often presents later in life w/ urinary infection, obstruction, stone, etc } 25% remain completely asymptomatic

What is the cause of supernumerary kidneys?

- second ureteral bud or branch off initial ureteral bud appears
- nephrogenic anlage divides into 2 separate metanephric tails
→ fragmentation of single metanephros or linear infarction producing separate viable fragments
- **2 ureteral buds interacts with 2 different metanephric blastema**

List the common features of a supernumerary kidney.

→ **usually below N kidney & generally smaller in size**

- **abN kidney or collecting system in 33%** } dilated collecting system + thinned cortex
→ obstructed ureter
- ~50% have completely independent ureters → rest have a common stem with a single orifice
→ **obeys Weigert-Meyer rule in 90%**
- abN vascular supply common

What associated anomalies are found with supernumerary kidneys?

- ectopic ureter of supernumerary kidney } uncommon
→ ipsilateral & contralateral native kidneys are N

ANOMALIES OF ASCENT

Simple renal ectopia

What is the epidemiology of renal ectopia?

- uncommon } **~1 in 500**
- **equal among M & F** → detected more often in F (more likely to get imaging – UTIs, etc)
- slightly **more common on L side**
- 10% have bilateral ectopia
- usually asymptomatic } can present with UTI, atypical renal colic, abdominal mass

What are the causes of renal ectopia?

- 1) ureteral bud maldevelopment
- 2) defective metanephric tissue
- 3) genetic abnormalities
- 4) maternal illnesses
- 5) teratogenic causes
- 6) vascular barrier

What are the potential locations of an ectopic kidney?

→ no single location is more common

- pelvic
- iliac
- abdominal
- thoracic (probably least common - 5%)
- contralateral or crossed

List the common features of an ectopic kidney?

- usually smaller
- may have abnormal shape (fetal lobulations)
- renal pelvis is usually anterior (instead of medial) } **rotation abnormality is very common**
- **56% have hydronephrosis** → 50% are due to obstruction } 70% UPJO
 } 30% UVJO
 → 25% due to VUR (grade 3-5)
 → 25% due to malrotation alone
- **30% have VUR**
- ureteric orifice found in N location
- abN renal vasculature common
- **genital anomalies occur in 15-45%** } bicornuate uterus, abN vagina, UDT, hypospadias, etc
- higher incidence of **contralateral renal anomalies** } **agenesis, VUR, obstruction**
- **20% have cardiac or MSK anomalies**
- very rarely see abnormally positioned or absent adrenal

Is the ectopic kidney at increased risk for disease?

- similar prognosis as N kidney } **except higher risk of stones, hydronephrosis, & trauma**
- no issue with pregnancy and vaginal delivery (dystocia very rare)

Cephalad renal ectopia

Which patient population get cephalad renal ectopia?

- patients with hx of omphalocele
 - contents herniate out into sac and kidneys continue to rise until stopped by diaphragm
 - **bilateral in all cases**
 - kidneys lie just beneath diaphragm
- asymptomatic and no impairment of urinary drainage

Thoracic kidney

What is a thoracic kidney?

- partial or complete protrusion of kidney above level of diaphragm **into posterior mediastinum**
- NOT from a congenital (Bochdalek) or traumatic diaphragmatic hernia

What is the epidemiology of a thoracic kidney?

- <5% of all patients with renal ectopia
- **~200 cases reported in literature**
- slight **L-sided predominance**
- more common in M → 2:1
- mostly asymptomatic

What is the cause of thoracic kidneys?

- kidneys normally in orthotopic position by 8wks gestation
- by this time, diaphragm is usually closed
- ? delayed closure of diaphragmatic anlage
- ? kidney overshoots usual position due to accelerated ascent

List the common features of a thoracic kidney?

- normally rotated
- N shape & size
- N collecting system → elongated ureter but never ectopic
- flimsy membrane of diaphragm covers kidney → **NOT within pleural space**
 - located in foramen of Bochdalek
- ipsilateral lung may be hypoplastic (compression from kidney)
- adrenal in N location
- N contralateral kidney
- no consistent anomalies in other organ systems

ANOMALIES OF FORM AND FUSION

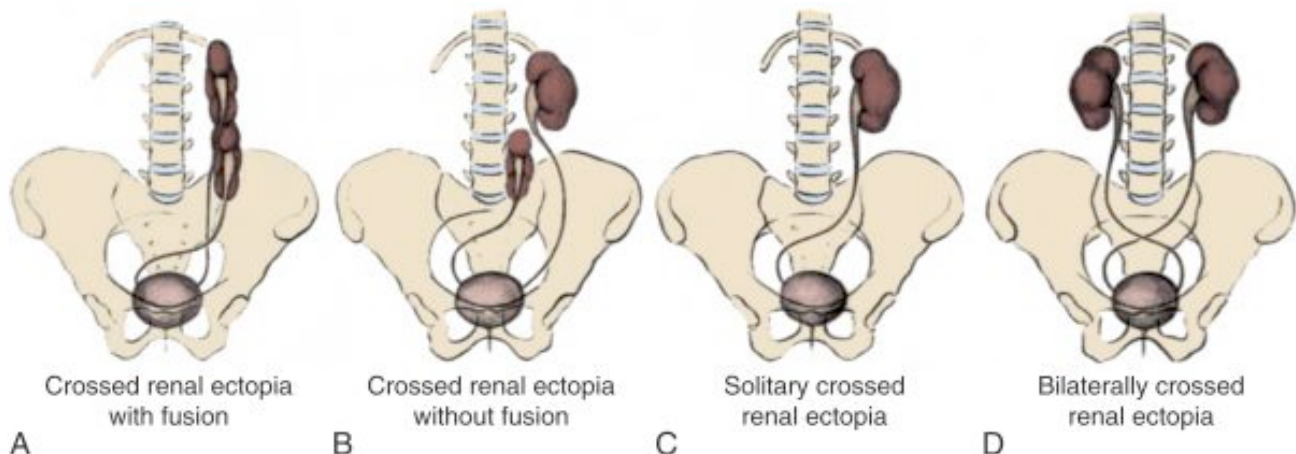
Crossed Renal Ectopia with and without Fusion

What is crossed renal ectopia?

- when kidney is located on opposite side from which its ureter inserts into bladder

What is the epidemiology of crossed renal ectopia?

- uncommon } ~1 in 1000 live births
- **90% are fused with ipsilateral kidney**
 - other than horseshoe, accounts for majority of fusion anomalies
 - **inferior ectopia with fusion most common**
 - superior ectopia is least common
- **10% are without fusion**
 - crossed ectopia without fusion
 - solitary crossed ectopia
 - bilaterally crossed ectopia (most rare of all crossed ectopia)
- generally a M predominance → 2:1
- generally **L-to-R ectopia more common** → 3:1
- usually have malrotated, lower lying kidney → asymptomatic in most (can have UTI or stone)



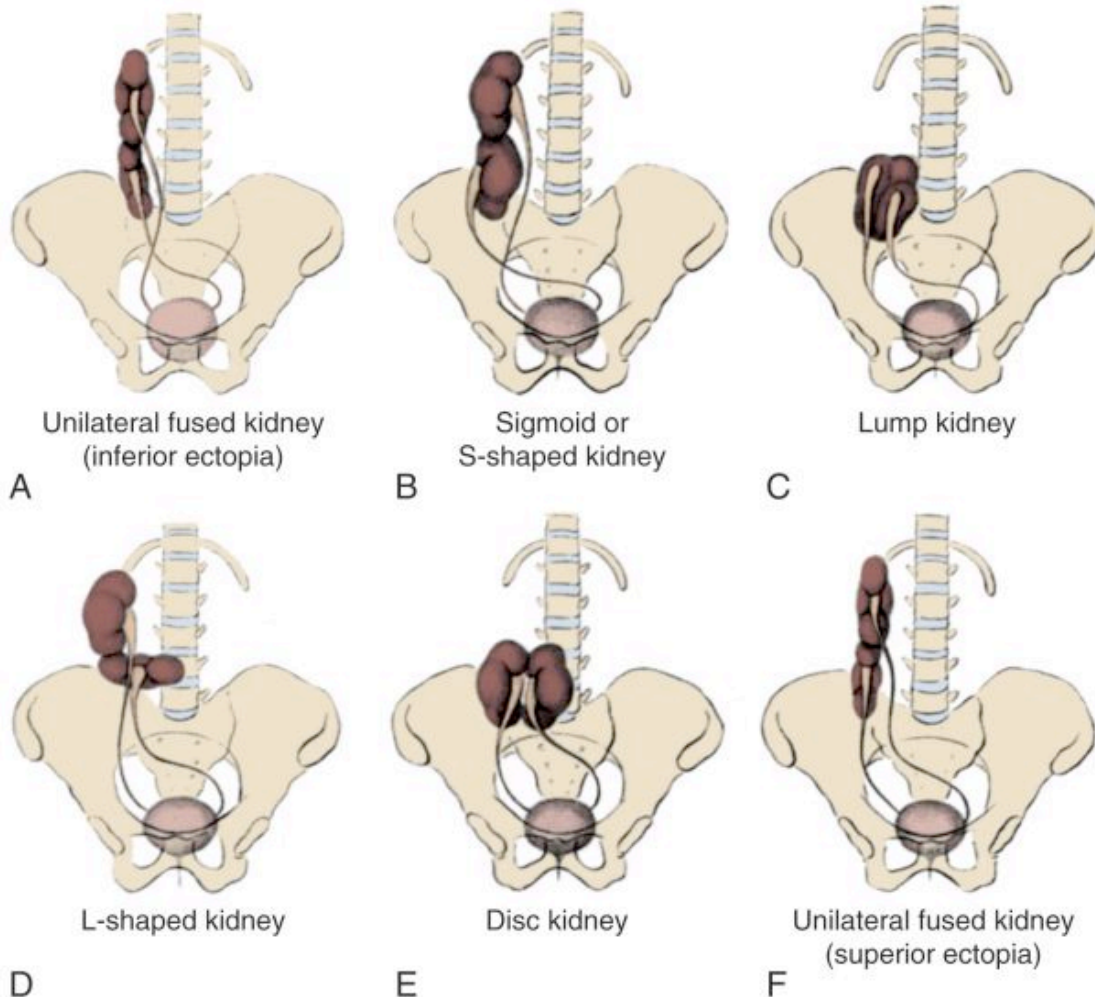
→ FORMS OF CROSSED RENAL ECTOPIA

**A → crossed renal ectopia w/ fusion most common

**C → solitary ectopic most common to have assoc'd anomalies

What are the different forms of fusion anomalies? } } } "I See Lumpy Logs Down South"

- 1) Inferior ectopia (most common)
 - 2) S-shaped or sigmoid
 - 3) Lump or cake
 - 4) L-shaped or tandem
 - 5) Disc or donut
 - 6) Superior ectopia
- \ only two forms that have crossing ureters



→ FORMS OF CROSSED RENAL ECTOPIA WITH FUSION

**A → by far the most common type

**F → least common type

What is the cause of crossed renal ectopia?

→ UNCLEAR

- ? abnormally placed umbilical artery pushes kidney to other side
- ? ureteral phenomenon → ureteral bud wanders over to other side and induces differentiation of contralateral nephrogenic anlage
- ? strong, undetermined forces determine path of renal ascent
- ? mal-alignment and abN rotation of caudal end of fetus
- ? genetic influence
- ? teratogenic factors
- final shape of fused kidneys depends on time and extent of fusion & degree of renal rotation
- ascent continues until N kidney reaches N position or until retroperitoneal structure prevents migration of fused mass
- no rotation occurs after fusion → can tell timing of fusion by rotation
→ ie anterior pelvis = early fusion

Are patients with crossed renal ectopia at increased risk for renal disease?

- slightly ↑'d risk of stones & infections

List the common features of crossed renal ectopia?

- ectopic kidney usually inferior to ipsilateral N kidney (inferior ectopia)
- **90% are fused with ipsilateral kidney**
- ureter of ectopic kidney always inserts on contralateral side & ureter of N kidney inserts on ipsilateral
- ureter from each kidney is usually orthotopic in all fusion anomalies
- can see hemitrigone or poorly developed trigone on side of ectopic kidney in solitary crossed ectopia
- **VUR found in ~20%** of crossed ectopic kidneys & 70% in bilateral crossed ectopia
- **UPJO found in 30%**
- can also find carcinoma in ectopic kidney
- abN renal vasculature common
- **anomalies most common with solitary renal ectopia**
 - genital abnormality in 40% } UDT or absence of vas
 } vaginal atresia or unilateral uterine abnormality
 } imperforate anus (20%)
 - MSK abnormality in 50%
 - otherwise low for other types of crossed ectopia

Horseshoe Kidney

What is a horseshoe kidney?

- 2 vertical renal masses on either side of midline, connected by an isthmus of parenchyma
 - **most common of all renal fusion anomalies**
 - almost every renal disease has been described in the horseshoe kidney

What is the epidemiology of the horseshoe kidney?

- [illegible]

What is the cause of a horseshoe kidney?

- UNCLEAR
- abnormality occurs **between 4th and 6th week of gestation**
 - after ureteral bud has entered renal blastema but **before rotation & ascent**
- something may push the developing metanephric masses together leading to contact & fusion
- fused kidney can't ascend into normal position and is **impeded by IMA**

List the common features of a horseshoe kidney.

- **anterior renal pelvis & ureters** that cross ventrally to isthmus
- **high inserted ureter** that passes anterior to isthmus
 - can also be **laterally displaced**
 - ureters are usually orthotopic
- **95% have isthmus at LP** → usually bulky parenchyma with own blood supply
 - can be flimsy midline fibrous tissue
 - isthmus usually located at L3-L4, just below IMA
- axis of each pelvis remains vertical or obliquely lateral
- calyces are N in number but atypical in orientation → **calyces point posteriorly**
- **variable blood supply** → only 30% have single renal artery
 - LP and isthmus can be supplied by IMA, common iliacs, external iliacs, sacral arteries, etc
- **20-30% have UPJO** → high insertion of ureter, passing anterior to isthmus, abnormal vessels
- **50% have VUR**
- **50% have urinary metabolic derangements**
 - hypercalciuria + hyperoxaluria + hypocitraturia + hypouricosuria

List GU and non-GU anomalies associated with horseshoe kidneys (CHART)

→ GU ANOMALIES

- genital → hypospadias 4%
 - UDT 4%
 - bicornuate uterus 7%
 - septate vagina 7%
- collecting system → **VUR 50%**
 - UPJO 20%
 - ureteral duplication 10%
- parenchymal → multicystic dysplasia 1%
 - AR PCKD 1%

→ NON-GU ANOMALIES

→ more common in kids w/ serious congenital anomalies

- CNS → NTDs
- CV → VSDs
- MSK

What syndromes are associated with horseshoe kidney?

- **Turner's syndrome (45,XO) → 10% - 60% (most common GU anomaly in Turner's)**
- Edward's syndrome (trisomy 18) → 20%
- Townes-Brock syndrome

Is the horseshoe kidney at increased risk of disease? }}} "SHUT"

- **Stones (not just from delayed drainage) → ~50%**
- **Hydronephrosis (obstruction)**
- **UTIs → 30%**
- **higher risk of renal Tumours**
 - } Wilm's tumour → 2x general population
 - usually on L (rarely in isthmus)
 - favorable histology (unless in isthmus)
 - } RCC → more common in isthmus BUT overall same risk as general popul.
 - **most common renal tumour in horseshoe**
- higher risk renal pelvic TCCs → ?related to chronic infection, obstruction, stones

ANOMALIES OF ROTATION

What is a malrotated kidney?

- when calyces don't point laterally and renal pelvis doesn't point medially
→ **usually associated w/ another renal anomaly } renal ectopia or horseshoe kidney**

What is the epidemiology of renal malrotation?

- **~1 in 500**
- more common in M (2:1) } no side predilection
- often seen in patients with **Turner's syndrome**

What is the cause of renal malrotation?

- UNCLEAR } thought to be related to unequal branching of ureteral bud in blastema

What are the 4 main malrotation anomalies of the kidney?

- named based on direction renal pelvis is facing } vessels used to understand malrotation

- 1) **ventral position** } pelvis faces anteriorly & calyces point posteriorly
→ no rotation has occurred
→ **most common form of malrotated kidney**
- 2) ventromedial position } pelvis faces anteromedial & calyces point posterolateral
→ incomplete rotation
- 3) dorsal position } pelvis faces posteriorly & calyces point anteriorly
→ over-rotation
→ rarest form of malrotated kidney
→ vessels come into hilus posteriorly
- 4) lateral position } pelvis faces laterally & calyces point medially
→ can be over-rotation OR reverse rotation
→ if vessels are anterior to kidney, then reverse rotation

List the common features of a malrotated kidney.

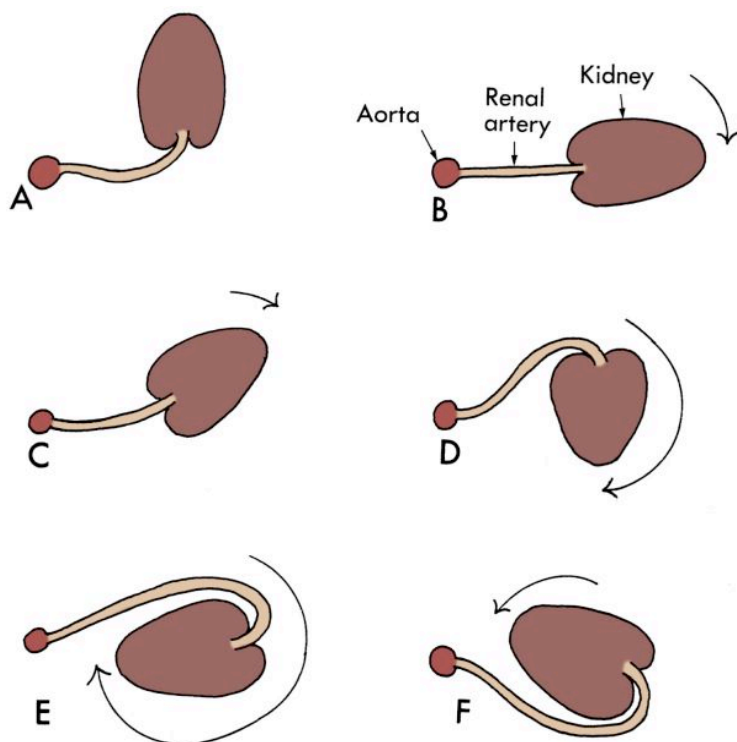
- **usually assoc'd w/ renal ectopia or horseshoe kidney** } B/L malrotation can be confused with horseshoe kidney
- abN shape } discoid, elongated, triangular or oval
- accentuated fetal lobulations
- dense fibrous tissue encases hilar area
- elongated & narrow renal pelvis with distorted UPJ
- upper ureter courses laterally } may also be encased in fibrous tissue
- varied blood supply } depends on direction & degree of rotation

How do malrotation anomalies of the kidney present?

- asymptomatic
- hydronephrosis } dull aching flank pain, Dietl's crisis, etc
- UTI
- hematuria

Is the malrotated kidney at increased risk of disease?

- normal renal function
- obstruction } fibrous encasement or compression from abN vessels
- infections
- stones



- A → embryonic position (hilus points ventral)
 B → N adult kidney
 C → incomplete rotation (hilus ventromedial)
 D → hyper-rotation (hilus dorsal)
 E → hyper-rotation (hilus lateral)
 F → reverse rotation (hilus lateral)

ANOMALIES OF RENAL VASCULATURE

Aberrant, Accessory, or Multiple Vessels

Define the terminology used for vascular anomalies

- multiple arteries → kidney supplied by more than 1 vessel
- accessory vessels → ≥ 2 arterial branches supplying same renal segment
- **aberrant (anomalous) vessels** → new arteries that originate from vessels other than the aorta or main renal artery

What is the epidemiology of renal vessel anomalies?

- **~80% have single renal artery**
- anomalies **more common on L**
- no sex or race predilection
- **true aberrant vessels rare** except in renal ectopia (w/ or w/o fusion) & horseshoe kidney
- usually asymptomatic } can present w/ obstruction (infundibulum, calyx, UPJ, etc), hematuria, UTI, stones

What is the cause of renal vessel anomalies?

- **represents a failure of complete degeneration of all primitive vascular channels**
- renal arterial tree derived from 3 groups of primitive vascular channels that coalesce to form the mature vascular pattern for all retroperitoneal structures
 - cranial group → 2 pairs that form phrenic artery
 - middle group → 3 pairs that form adrenal artery
 - caudal group → 4 pairs that form main renal artery

What is the arterial & venous blood supply of the kidney?

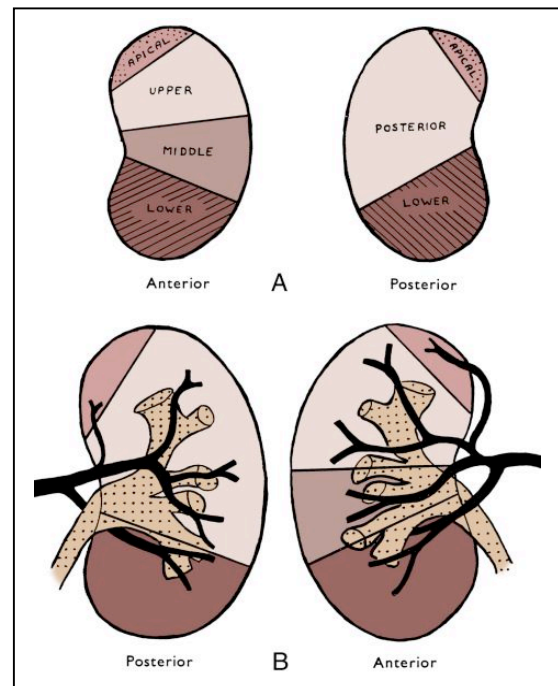
Arterial	Venous
→ all are end arteries	→ collateral drainage
- segmental (anterior and posterior)	- efferent arteriole
- lobar	- vasa recta
- interlobar	- interlobular (communicate freely)
- arcuate	- arcuate
- interlobular	- interlobar
- afferent arteriole	- lobar
	- segmental

What are the vascular territories of the kidney?

- lobes of Graves
- anterior branch } **apical (greatest variation)**
 - } upper
 - } middle
 - } lower
- posterior branch (least variation)

What are the different origins of the apical segmental artery?

- 1) **anterior division (43%)**
- 2) jxn of anterior and posterior (23%)
- 3) main renal artery or aorta (23%)
- 4) posterior division (10%)



Which area is the best way to access the collecting system without encountering vessels (ie PNL)?

- directly end-on through fornix
- inferiorly on posterior aspect of pelvis

When performing an endopyelotomy for UPJO, where should the incision be made?

- laterally and posteriorly
- inferior branch of renal vein on anterior aspect of renal pelvis in 40% of kidneys

Is a kidney with renal vessel anomalies at increased risk for disease?

- NO affect on renal function in most cases
- obstruction of collecting system, stones, UTIs, very uncommon

What are the IVP features suggestive of multiple or aberrant renal vessels?

- 1) filling defect in renal pelvis consistent with anomalous vascular pattern
- 2) hydronephrosis + sharp cutoff in superior infundibulum
- 3) UPJO + angulated ureter near renal pelvis + kidney axis more vertical than normal
- 4) differences in timing & concentration of one renal segment or entire kidney cf other kidney

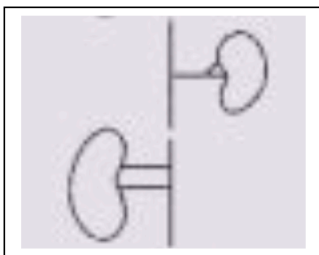
What is the most common arterial anomaly in the kidney?

→ single renal artery is the most common (70-80%)

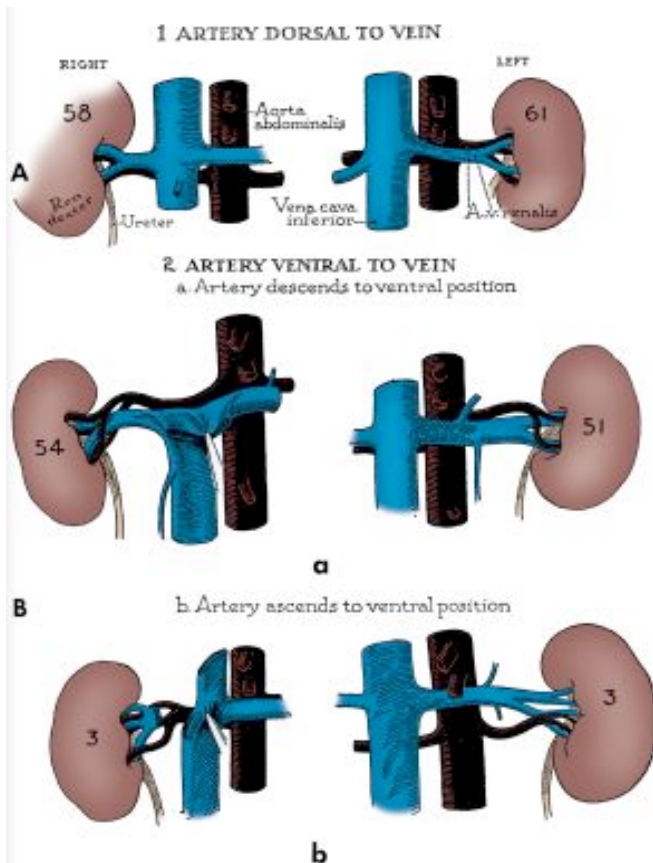
- 1) 1 hilar main artery + 1 upper pole branch (12.5%) } **most common on L**
2) 2 hilar arteries (10.8%)

What is the most common arterial-venous relationship in the kidney?

- 1) artery posterior to vein (47.6%)
- 2) artery ventral to vein } from above (42%)
 } from below (2.4%)



→ MOST COMMON RENAL ARTERIAL ANOMALIES



→ MOST COMMON ARTERIAL-VEIN RELATIONSHIPS IN KIDNEY

Renal Artery Aneurysm

What is the epidemiology of renal artery aneurysms?

- **0.1% to 0.3% incidence**
- congenital vs acquired
- **associated with AD PCKD**
- **slightly more common on R side**
- bilateral in 15%
- mostly asymptomatic → especially in kids (50%)
→ in adults can see HTN (55%), hematuria (30%), pain (15%)

What are the different types of renal artery aneurysms?

- 1) saccular → >90% (more common than in adults – 75%)
- 2) fusiform → congenital (at branch point)
- 3) dissecting
- 4) intrarenal

What are the acquired causes of renal artery aneurysms?

- inflammatory
- traumatic
- degenerative

What signs are suspicious for renal artery aneurysm?

- pulsatile mass in region of renal hilum
- bruit over renal artery
- wreath-like calcification in area of renal artery or its branches (30%) on AXR

What are the indications for surgery for a renal artery aneurysm in children?

- 10% spontaneous rupture rate dictates management
- 1) poorly controlled HTN
- 2) incomplete ring-like calcification present
- 3) aneurysm >2.5cm
- 4) >1cm in female patient of child-bearing age (higher incidence of rupture during pregnancy)
- 5) increasing size on serial imaging
- 6) **if an AVF is present**

What are the indications for surgical removal of renal artery aneurysms? } WEBBERRR'S DIC

- 1) **W**oman of childbearing age who is likely to conceive
- 2) **E**mbolization from thrombus with aneurysm on angio
- 3) **B**igger than >2cm + other RF for rupture
- 4) **B**P uncontrolled
- 5) **E**xpanding on imaging
- 6) **R**enal ischemia
- 7) functionally significant **R**AS
- 8) **R**uptured
- 9) **S**ymptoms (flank pain, hematuria)
- 10) **D**issecting aneurysm
- 11) **I**ncomplete **C**alcification

Renal AV Fistula

What are the 2 types of renal AVFs?

- 1) congenital → account for <25%
→ cirroid configuration with multiple communications b/w the main or segmental renal arteries and venous channels
- 2) acquired → increasing incidence
→ secondary to trauma, inflammation, renal Sx, or perc needle Bx
→ often disappears spontaneously after several months

What is the epidemiology of congenital renal AVFs?

- usually present in 3rd or 4th decade
- more common in F → 3:1
- **more common on R side**
- most commonly in **UP (45%)**, least common in lower pole (25%)

What are the signs & symptoms of a renal AV fistula?

- renal bruit (75%)
- hematuria (75%)
- HTN (40-50%) } renin-mediated
- LV hypertrophy & high-output cardiac failure (50%)
- abdo or flank pain
- diminished or absent function in affected segment
- filling defect in collecting system (clot or encroachment by fistula)

What are the indications for surgery for a renal AV fistula? }} “CHHERR”

- **C**ardiac failure
- uncontrolled **H**TN
- ongoing **H**ematuria
- **E**xpanding lesion on imaging
- **R**etroperitoneal bleed (acute)
- **R**enal failure (progressive)

What are the options for management of a renal AV fistula?

- selective embolization
- balloon catheter occlusion
- vascular ligation
- partial Nx
- nephrectomy

ANOMALIES OF THE COLLECTING SYSTEM

What are the different anomalies of the upper GU collecting system?

- calyx & infundibulum
 - } calyceal diverticulum
 - } hydrocalycosis
 - } megacalycosis
 - } unipapillary kidney
 - } extra-renal calyces
 - } anomalous calyx (renal pseudotumour) → hypertrophied column of Bertin
 - } infundibulopelvic dysgenesis
- pelvis
 - } extra-renal pelvis
 - } bifid pelvis

Calyx and Infundibulum

What is a CALYCEAL DIVERTICULUM?

- cystic cavity **lined by transitional epithelium**, encased w/in renal parenchyma, and peripheral to a minor calyx
 - connected to minor calyx by narrow channel



→ RETROGRADE SHOWS MULTIPLE CALYCEAL DIVERTICULA

What is the epidemiology of calyceal diverticula?

- 4.5 per 1000 (0.45%)
- most common in **upper calyces** } **thin parenchyma overlies diverticulum**
- no predilection for side or sex

What are the 2 types of calyceal diverticulum?

- type 1 → adjacent to calyx
→ most common type
- type 2 → communicates with renal pelvis directly
→ larger
→ tend to be symptomatic ones

What is the cause of calyceal diverticula?

- congenital factors → similar incidence in kids & adults
- acquired factors → ? localized cortical abscess draining into a calyx
→ ? obstruction secondary to stone formation or infection within calyx
→ ? progressive fibrosis of infundibular stenosis
→ ? renal injury
→ ? achalasia or dysfxn of supposed “sphincter” surrounding a minor calyx

What are the complications of having a calyceal diverticulum?

- all complications of urine stasis & obstruction
- **stones } ~40% develop stones**
- infection
- milk of calcium (crystallized calcium salts without actual stone formation)

What is the best test to evaluate a calyceal diverticulum?

- IVP or CT with delayed films

What are some associated findings of calyceal diverticulum?

- **VUR in up to 2/3**

What are the indications for surgery for a calyceal diverticulum?

- 1) persistent pain
- 2) recurrent/resistant UTIs
- 3) hematuria
- 4) milk of calcium or true stone formation
- 5) progressive renal damage

Which patients with asymptomatic calyceal stones should be treated?

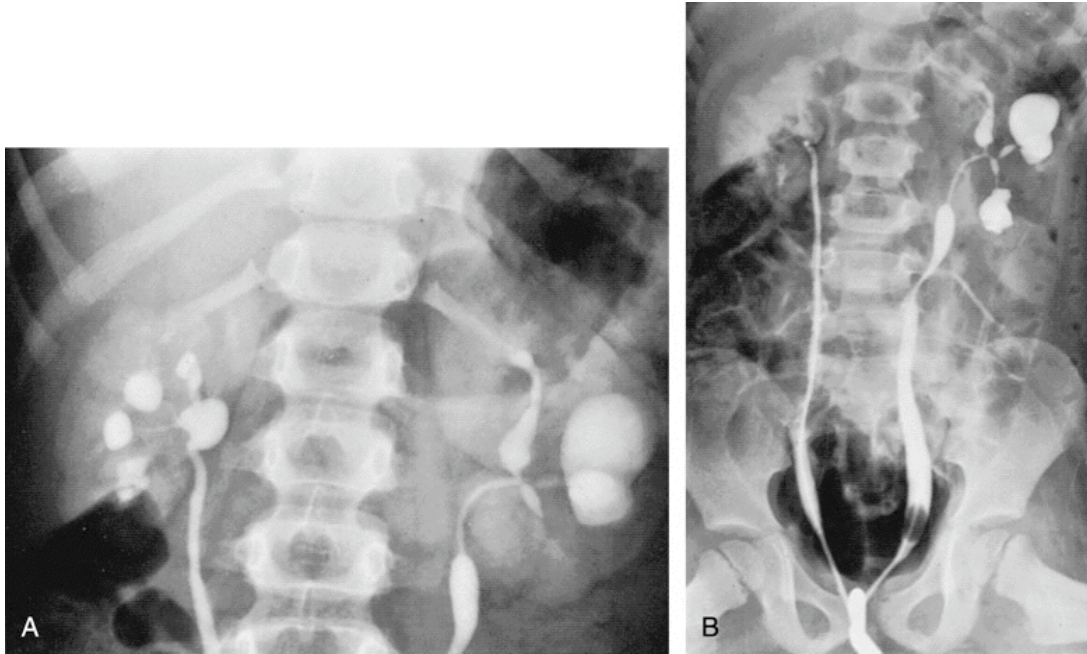
- 1) kids
- 2) patients with solitary kidney
- 3) high-risk professions (eg pilots)
- 4) women considering pregnancy

What are the surgical management options for a calyceal diverticulum?

- partial Nx → a thing of the past
- percutaneous stone removal + ablation of mucosal surface & diverticular neck
- retrograde ureteroscopic enlargement of diverticular neck + removal of stones
- laparoscopic stone removal + marsupialization of diverticulum

What is HYDROCALYCOSIS?

- **very rare cystic dilatation of a major calyx due to obstruction**
→ demonstrable connection to renal pelvis } **lined by transitional epithelium**
- N number of calyces



→ HYDROCALYCOSIS OF INFUNDIBULOPELVIC STENOSIS

A → right infundibular and left infundibulopelvic stenosis

B → retrograde showing mildly dilated left ureter with diffuse tubular backflow on right

What is the cause of hydrocalycosis?

- congenital or acquired intrinsic obstruction (eg infundibulopelvic stenosis)
- dilation of upper calyx due to obstruction of upper infundibulum by vessels or stenosis
- achalasia of the ring of muscle at the entrance of the infundibulum into the renal pelvis

What is the DDx of hydrocalycosis?

- caliectasis from ureteral obstruction
- renal TB
- large calyceal diverticulum
- megacalycosis
- calyceal clubbing from recurrent pyelonephritis or medullary necrosis

What is the management of hydrocalycosis?

- depends on cause
- if due to vascular obstruction (eg Fraley's syndrome) → dismembered infundibulopyelostomy
- if due to intrinsic stenosis of infundibulum → intubated infundibulotomy or partial Nx
→ percutaneous approach is today's standard
- usually see clinical improvement but radiological appearance not often altered

What is MEGACALYCOSIS?

- **NON-obstructive enlargement of calyces from malformation of the renal papillae**



→ BILATERAL MEGACALYCOSIS

A → left sided megacalycosis

B → note dilated distal ureter with normal caliber upper ureter

What is the epidemiology of megacalycosis?

- more common in M → 6:1
- **only found in whites**
- bilateral disease in M, unilateral disease in F
- not familial

What is the cause of megacalycosis?

→ **most likely congenital**

- ? early obstruction that is relieved, but dilated fetal calyces retain their obstructed appearance
- ? primary hypoplasia of juxtamedullary glomeruli

What are the features associated with megacalycosis?

- calyces are dilated, malformed, and **increased in #**
- renal pelvis is NOT dilated & does NOT have thickened wall
- normal UPJ
- overlying parenchyma is N in thickness + no signs of scarring or chronic inflammation
- **underdeveloped medulla** → falciform crescent appearance instead of normal pyramidal shape
- abnormal cortical collecting tubules
- there may be segmental dilatation of distal third of ureter

Are there any long term sequelae of megacalycosis?

- no progression of anatomic derangement or functional impairment of kidney
- **mild concentrating defects** have been reported

What is a UNIPAPILLARY KIDNEY?

- very rare anomaly } 18 cases
- **solitary calyx draining single papilla**
 - due to failure of progressive branching after first 3 to 5 generations of the ureteral bud
 - renal pelvis created during first 3-5 generations of branching

What are the features of a unipapillary kidney?

- solitary calyx drains a ridge-like papilla
- Bx reveals **glomerulosclerosis**, tubular atrophy, and increased fibrosis
- kidney is usually smaller than N and function if often reduced
- **opposite kidney is often absent**
- **genital anomalies are often present**
- often see abnormalities of proximal ureter → megaureter, VUR, ectopic insertion

What are EXTRA-RENAL CALYCES?

- uncommon congenital anomaly where the **major calyces & the renal pelvis are outside the parenchyma of the kidney**

What are the features of a kidney with extrarenal calyces?

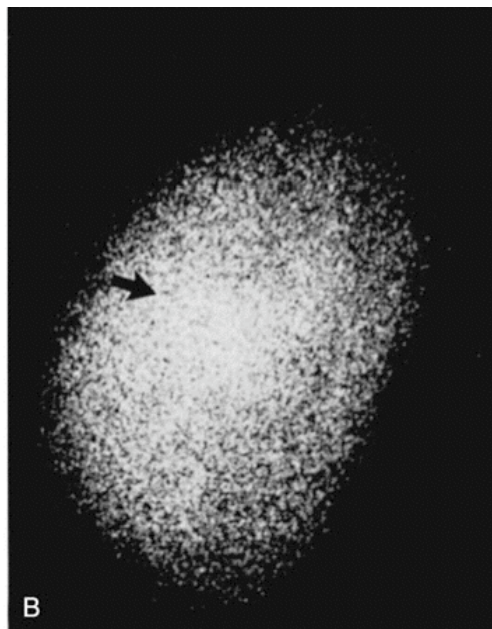
- **anomalous distribution of vessels** → usually at circumferential edge of flat, widened hilum
- usually discoid shaped kidney
- usually asymptomatic → stasis can lead to infection and stones
- sometimes calyces are blunted → so may seem like obstruction or pyelo

What is a HYPERTROPHIED COLUMN OF BERTIN?

- aka pseudotumour of kidney
- manifests as localized mass situated **b/w infundibula of upper & middle calyceal groups**
- may be large enough to compress and deform the adjacent pelvis and calyces
 - individual calyces are normal though
- **renal scan shows N uptake**
- **U/S shows normal echogenic pattern of parenchyma**



→ HYPERTROPHIED COLUMN OF BERTIN
A → mass effect with splaying of middle calyces



B → normal uptake on renal scan

What is INFUNDIBULOPELVIC STENOSIS?

- forms a link between cystic dysplasia of the kidney & the grossly hydronephrotic kidney
- **varying degrees of infundibular or infundibulopelvic stenosis that may be associated with renal dysplasia**

What are the associated features of infundibulopelvic stenosis?

- usually bilateral
- **commonly associated with VUR**
- patients usually present with infection, HTN, or flank pain
- normal function (or only slightly affected) despite extensive dysmorphic kidney features

Are patients with infundibulopelvic stenosis at increased risk for disease?

- calyceal stones
- infections
- HTN
- long term f/u reveals that progressive renal deterioration is common

Pelvis

What is the clinical relevance of an extrarenal pelvis?

- only of clinical importance when drainage is impaired
- can be associated with malposition, malrotation → predisposes to stasis, infection, and stones

What is the significance of a bifid pelvis?

- approximately 10% of N renal pelves are bifid
 - should be considered variant of normal
- no increased incidence of disease
- may see 'yo-yo effect' on renal scan
 - urine ascending one limb after descending from another

*** anomalies that have side predilection are more common on L side
EXCEPT renal AVM and renal artery aneurysms ***

*** most anomalies are associated with stones, hematuria, UTIs ***

Chapter #114 – Renal Dysgenesis and Cystic Kidney Disease

MOLECULAR GENETICS

RENAL AGENESIS

What is the cause of renal agenesis?

- can occur secondary to defect in any one of several structures
 - wolffian duct
 - ureteric bud
 - metanephric blastema

What is Potter's syndrome?

- bilateral renal agenesis } only ~500 cases reported
- **more common in M**
- early death due to pulmonary hypoplasia from oligohydramnios } NOT from lack of renal tissue
- Potter's facies } hypertelorism
 - } prominent inner canthal folds
 - } recessive chin
- orthopedic defects from intrauterine compression (large claw hands, bowed, clubbed feet, etc)
- usually sporadic and associated with other congenital anomalies (eg UG sinus defects)
- RFs include +ve FmHx and ↑'d maternal age

How common is unilateral agenesis?

- more common } 1 out of every ~1000 births
 - often associated with ipsilateral malformations of wolffian duct or mullerian duct structures
 - uterine horn or fallopian tube, ovary, testis, vas deferens, seminiferous tubules
 - also associated with other urologic abN'ities in ~50%
 - **VUR in ~30%**
 - obstructive megaureter in ~10%
 - UPJO in ~5%
- \ } similar to rates associated with unilateral MCDK
/ → may represent involuted MCDK

What is Mayer-Rokitansky-Kuster-Hauser syndrome?

- unilateral renal agenesis (or renal ectopia) + ipsilateral mullerian defects + vaginal agenesis

DYSPLASIA

What is renal dysgenesis?

- **maldevelopment of the kidney that affects its size, shape, or structure**
- **3 main types of dysgenesis:**
 - a) **dysplastic** (eg obstruction, VUR)
 - b) **hypoplastic** (eg Ask-Upmark, oligomeganephronia)
 - c) **cystic** (eg Genetic – VHL, TS; Sporadic – MCDK, ARCD)
- dysplasia is always accompanied with hypoplasia BUT hypoplasia can exist alone
- aplastic dysplasia is represented by a nubbin of nonfunctioning tissue (not necessarily reniform) that meets histologic criteria for dysplasia

What is renal dysplasia?

- **leading cause of renal failure in kids**
- no universal definition
- a histologic diagnosis } presence of embryonic mesenchyme + primitive renal components
- **metanephric development starts but doesn't or can't finish**
- common features include:
 - distorted renal architecture
 - immature or primitive glomeruli
 - nephron precursors (comma and S-shaped bodies)
 - **Hallmark is "primitive ducts" } duct encircled by collars of fibromuscular cells**
 } ?remnant of ureteric bud
 - **cartilage seen on micropathology**
 - cysts may or may not be present
- **2 main types of renal dysplasia**
 - a) altered genetic pathway that leads to abN development of nephron or collecting duct
 - b) obstruction

What are some of the associations to renal dysplasia?

- [illegible]

What is familial renal adysplasia?

- when all or part of a group of renal anomalies is seen in one family
 - 1) renal agenesis
 - 2) renal dysplasia
 - 3) MCDK
 - 4) renal aplasia
- AD inheritance

HYPOPLASIA AND HYPODYSPLASIA

What is the classification of renal hypoplasia and hypodysplasia?

→ hypoplasia

- true “oligonephronia”
 - with N ureteral orifice
 - with abN ureteral orifice
- oligomeganephronia
- segmental (Ask-Upmark kidney)

→ hypodysplasia

- with ectopic ureteric orifice (more common)
 - lateral ectopia
 - medial or caudal ectopia w/ ureterocele
- with N ureteric orifice (less common)
 - with or without obstruction
- with urethral obstruction
- prune-belly syndrome

What is renal hypoplasia?

- **kidney with ↓'d number of calyces & nephrons, but is otherwise N**
 - **NOT dysplastic nor embryonic**
- may be unilateral or bilateral
 - if unilateral, contralateral side shows compensatory growth
- may be associated with VUR } reflux nephropathy
 - segmental hypoplasia (Ask-Upmark kidney) is likely a type of reflux nephropathy
- may also be associated with ectopic ureters

What is oligomeganephronia?

- **marked reduction in number of nephrons + hypertrophy of each nephron**
 - elongated, widened nephrons
- usually bilateral condition and is associated with low birth weight
- affects boys more often than girls (3:1)
- presents with vomiting, dehydration, intense thirst, polyuria (low specific gravity)
- abN GFR but stays stable for yrs } can get severely retarded growth
- marked proteinuria & deterioration of renal function occurs in early teen yrs
- small kidneys
- nephrons are elongated and widened at proximal end

Rx → high fluid intake

- correction of salt loss and acidosis
- limit dietary protein to 1.5g/kg
- dialysis and renal Tx for ESRD

What is an Ask-Upmark kidney?

- **smaller than N kidney + segmental hypoplasia**
 - **usually associated with VUR + severe HTN**
 - likely not a developmental lesion but an **acquired lesion** } **reflux +/- infection**
 - may occasionally find some areas of dysplasia
 - HTN'sive encephalopathy & retinopathy can occur
 - if disease is bilateral, there may be some renal insufficiency
- Rx → control of HTN
- correction of VUR may prevent further renal damage but usually has no effect on HTN
 - for unilateral disease } partial or total nephrectomy
 - failure may indicate unrecognized scar or generalized arteriosclerosis in remaining kidney
 - for bilateral disease } medical mgt until dialysis and/or renal Tx needed

What is renal hypodysplasia?

- **usually occurs with ectopic ureters**
 - extent of dysplasia usually correlates with degree of ectopia
 - often see ectatic, rounded calyces } not same as from VUR
 - **lateral ectopia** } **usually associated with VUR**
 - **medial or caudal ectopia** } **may have ureterocele**
- can also occur with N ureteral orifices
 - with obstruction } primary obstructive megaureter, UPJO, etc
 - without obstruction
- can be associated with urethral obstruction (eg PUVs) or Prune-Belly syndrome
 - Prune-Belly syndrome } absent abdominal musculature
 - } various degrees of renal dysplasia, wide & tortuous ureters, large and laterally placed orifices
 - lower urinary tract usually not obstructed
 - } UDT

CYSTIC RENAL DISEASE

What are renal cysts?

- can be ectatic tubules or collecting duct, a diverticulum of the nephron, or an isolated sac
- usually arise from nephrons & collecting ducts after they have formed
 - MCDK is an exception, as it arises before formation of the nephron
 - benign multilocular cyst is another exception, as it represents neoplastic growth
- can be located diffusely in the kidney or in one segment only
- may represent a form of dysplasia or be accompanied by some dysplasia
- may have different features
 - **AD PCKD, TS, VHL, acquired renal cystic disease } cysts w/ hyperplastic lining**
 - **AR PCKD & MSK } cysts are actually ectatic collecting ducts**

How are renal cystic diseases classified (CHART)?

→ GENETIC (“MC Jafa Man”)

- Multiple malformation syndromes with renal cysts (eg TS, VHL)
- Congenital nephrosis (“familial nephrotic syndrome”) (AR)
- Juvenile nephronophthisis (AR)
- AD PCKD (“adult”)
- Familial hypoplastic glomerulocystic disease (AD)
- AR PCKD (“infantile”)
- Medullary cystic disease (AD)

→ NON-GENETIC (“MB MASS-D”)

- MCDK
- Benign multilocular cyst (cystic nephroma)
- MSK
- Acquired renal cystic disease (ARCD)
- Simple cysts
- Sporadic glomerulocystic kidney disease
- calyceal Diverticulum (pyelogenic cyst)

What is the difference between multicystic and polycystic?

- multicystic } refers to a dysplastic entity
- polycystic } refers to several conditions, mostly inherited, all w/o dysplasia, and all w/ nephrons throughout the kidney

What is the DDx of bilateral renal cystic disease?

- AR PCKD (manifests any time from in utero to age 20yrs)
- AD PCKD (from in utero to autopsy)
- Tuberous Sclerosis (from in utero to usually before age 30)
- VHL disease (rare in the first few yrs of life but almost always before age 30)
- bilateral simple cysts (usually after age 35)
- acquired renal cystic disease (after ESRD develops)

Table 114-4 -- Sonographic Differential Diagnosis of a Newborn with Bilateral, Large, Cystic Kidneys

Homogenous, Hyperechogenic Kidneys Without Macrocysts	With Diffuse Macrocysts
Autosomal recessive polycystic kidney disease (characteristic appearance)	Autosomal recessive polycystic kidney disease (atypical appearance)
Autosomal dominant polycystic kidney disease (atypical appearance)	Autosomal dominant polycystic kidney disease (characteristic appearance)
Sporadic glomerulocystic kidney disease	Sporadic glomerulocystic kidney disease
Contrast nephropathy	Tuberous sclerosis
Renal vein thrombosis	

What are the characteristic features of the different forms of renal cystic diseases?

→ **GENETIC DISEASES } } } "MC Jafa Man"**

- 1) **AR PCKD** } **chromosome 6**
 - } usually large, homogeneous, echogenic kidneys with cysts of collecting duct
 - **USUALLY NO DISCRETE CYSTS (microcystic)**
 - } associated with congenital hepatic fibrosis biliary dysgenesis
- 2) **AD PCKD** } **90% PKD1 (chromosome 16), 10% PKD2 (chromosome 4), <1% PKD3**
 - } large kidneys with scattered renal cysts throughout
 - } associated with berry aneurysms, diverticulitis, renal artery aneurysms, MV prolapse, & cysts in the kidney, liver, spleen, pancreas, lung, arachnoid, pineal gland, SVs
- 3) **Juvenile nephronophthisis/medullary cystic disease complex**
 - juvenile nephronophthisis } **AR (chromosome 2)**
 - } cysts at corticomedullary jxn that develop AFTER onset of ESRD
 - Senior-Loken syndrome } **AR**
 - } cysts at corticomedullary junction
 - } associated with retinitis pigmentosa
 - Medullary cystic disease } **AD**
 - } cysts at corticomedullary jxn that develop BEFORE onset of ESRD
- 4) **Congenital nephrosis** } **chromosome 19**
 - } dilatation of PCT with diffuse hypertrophy of podocytes
 - } 2 types → Finnish type
 - diffuse mesangial sclerosis type (assoc'd with Denys-Drash)
- 5) **Familial glomerulocystic kidney disease** } small or normal sized kidneys
 - } glomerular cysts
- 6) **Multiple malformation** a) **TS** } **AD** → **TSC1 (chromosome 9 - hamartin)**
 - **TSC2 (chromosome 16 - tuberin)**
 - } cysts and AMLs throughout kidney
 - } assoc'd w/ mental retardation, skin adenoma sebaceum, epilepsy, cranial tubers, Ash-Leaf spots, Shagreen patch, pheo
 - } ?increased risk of RCC

b) **VHL** } **AD (chromosome 3p25)**
 - } renal cysts, adenomas, and clear cell RCC
 - } assoc'd w/ cerebellar hemangioblastomas, retinal angiomas, pancreatic cysts, pheo, epididymal cystadenomas

→ **NON-GENETIC DISEASE } } } "MB MASS-D"**

- 1) **MCDK** } renal maldevelopment w/ diffuse cysts and remnants of early metanephric development
- 2) **Benign multilocular cyst** } benign cystic tumour of kidney (rest of kidney is N)
 - } more common in boys when younger and women when older
- 3) **MSK** } ectatic collecting duct with rest of nephrons fairly normal
- 4) **Acquired renal cystic disease** } diffuse cysts and adenomas
 - } increased risk of RCC (usually papillary)
 - } incidence increases with duration of ESRD
- 5) **Simple cysts** } single or multiple cysts (rest of kidney N)
 - } very common with increasing age
- 5) **Sporadic glomerulocystic kidney disease** } large kidneys w/ predominantly glomerular cysts
 - } associated with biliary dysgenesis (10%)

AR PCKD (“INFANTILE”)

What is the genetic abnormality associated with AR PCKD?

- PKHD1 gene on **chromosome 6** } protein fibrocystin (aka polyductin)

What is the usual presentation of AR PCKD?

- **usually presents perinatally** } most severe forms appearing earliest in life
 } milder forms present later in childhood, rarely in early 20's
- **50% of affected newborns die within first few days of life (PERINATAL type)**
 - large abdominal masses may make delivery difficult
 - get oligohydramnios, pulmonary hypoplasia, Potter's facies, etc
 - uremia & respiratory failure
 - 50% of those that survive neonatal period are alive at 10yrs of age
- **the earlier the presentation the more severe the renal disease**
- **all patients have varying degrees of congenital hepatic fibrosis** (biliary ectasia)
 - the younger the patient presents with AR PCKD, the milder the liver disease
 - the younger the patient presents with liver disease, the milder the renal disease
- **kids that present later in life develop renal failure & HTN more slowly (JUVENILE type)**
 - liver failure is the main issue in these kids
- **discrete cysts not present when disease manifests early** } can appear as kid gets older
- affected newborns have **dilated collecting ducts** that radiate to the outer margin of the kidney

What does AR PCKD look like on U/S imaging?

- early manifestation } bilaterally enlarged kidneys
 - } hyperechoic cortex (microcysts)
 - ↑'d echogenicity due to multiple interphases created by dilated ducts
 - } reniform shape
 - } peripheral sonolucent rim (compressed cortex)
 - } macrocysts are rare in newborns
- later manifestation } presence of discrete cysts more common w/ increasing age of presentation
 - usually <1cm & not very large
- non-renal findings } hepatomegaly
 - } splenomegaly
 - } congenital hepatic fibrosis
 - } biliary dysgenesis

What does AR PCKD look like on IVP imaging?

- functioning kidneys w/ **characteristic radial or medullary streaking (“sunburst” pattern)**
 - caused by dilated collecting tubules filled with contrast medium
 - contrast may be present up to 48hrs later
- calyces, renal pelvis, and ureter are usually NOT visible
- may or may not show functioning kidneys

What is the management of AR PCKD?

- referral for genetic counseling } parents should not have disease
 } all siblings have 1 in 4 chance of getting disease
- early respiratory care
- those that survive will need treatment for HTN, CHF, renal failure & liver failure
 → portal HTN, esophageal varices, hemodialysis, etc

What is Caroli's disease?

- AR PKCK that presents with large echogenic cystic kidneys with slower deterioration of renal function
- live long enough to develop hepatic & pancreatic cystic disease

AD PCKD (“ADULT”)

What is the genetic abnormality associated with AD PCKD?

- **AD inheritance with ~100% penetrance**
- + genetic imprinting (worse if from mom) AND + genetic anticipation (earlier presentation in kids)
- 90% involve chromosome 16 (PKD1) } polycystin-1
- 10% involve chromosome 4 (PKD2) } polycystin-2
- } usually milder form of disease with later presentation
- <1% involves abnormality in PKD3 } unknown gene location

What is the usual presentation of AD PCKD?

- **most cases present between age 30 and 50yrs of age**
 - has been recognized in newborns
 - early presentation associated with more aggressive disease (eg stillbirth)
 - **50% that manifest disease in utero or in infancy have macrocysts**
- usually presents with flank pain, GI symptoms, HTN, proteinuria, hematuria, stones, etc
 - **HTN is the most common presentation**
 - 50% have hematuria
 - 20-30% develop stones
- asymptomatic presentation more common now with increased screening
- **usually bilateral presentation**
- renal failure seldom seen before age 40, unless it presented in infancy
 - anemia not common even if ESRD due to increased epo levels
 - once renal volume quadruples (1500 cc), GFR declines rapidly
- >10x more common than AR PCKD
- **large, cystic kidneys that are sometimes asymmetrical**
 - cysts derived from entire nephron
- **usually don't have any hepatic fibrosis but can get liver cysts**

List anomalies commonly associated with AD PCKD }}} Be DA Real MVP w/ 8 aCYSTs

- circle of Willis “Berry” aneurysms (10-40%) } ~10% of patients die because of SAH
 - Diverticulitis
 - Aortic arch aneurysms
 - Renal artery aneurysms
 - MV Prolapse
 - cysts of the kidney liver, spleen, pancreas, lung, pineal gland, arachnoid, SVs
 - hepatic cysts more common in adults and in F } usually asymptomatic
- ➔ **NOT ASSOCIATED WITH AN INCREASED RISK OF RCC**
- when present, however, more often B/L, multicentric, and sarcomatoid variant more common

What is the histopathology of the renal cysts found in AD PCKD?

- **diffuse macrocysts ranging from few mm's to a few cm's** } only 1% of nephrons develop cysts
→ found throughout cortex and medulla
- **epithelial hyperplasia of cyst lining with hyperplastic polyps**
→ similar to VHL, TS, ARCD

How is the diagnosis of AD PCKD made?

- **look for family history } renal cysts, renal disease, HTN, strokes**
- if no family hx, presumptive diagnosis made if bilateral renal cysts and ≥ 2 of the following:
 - bilateral renal enlargement
 - ≥ 3 hepatic cysts
 - cerebral artery aneurysms
 - solitary cyst of the arachnoid, pineal gland, pancreas, or spleen

What does AD PCKD look like on imaging?

- IVP } bilaterally enlarged kidneys + stretched calyces
 - } bubble or Swiss cheese appearance in nephrogram phase
 - } may resemble AR PCKD ("sunburst" - medullary streaking)
- CT and MRI } may be better than U/S
 - } CT may show enlarged kidneys with macrocysts (+/- hemorrhage & calcifications)
 - } MRI good for those with renal insufficiency (risk of NSF)

What are the potential renal complications of AD PCKD?

- renal failure
- stones
- HTN
- flank pain
- pyelonephritis
- perinephric abscesses
- hematuria

What are the RFs for progression of AD PCKD to ESRD?

- M gender
- early age at presentation
- PKD1 gene (chrom. 16)
- HTN
- Blacks
- presence of gross hematuria

What is the management of AD PCKD?

- renal involvement more common in M } earlier CRF and HTN
- hepatic cysts more common in F
- 1) genetics counseling
 - AD inheritance (50% of affected adults children will have disease)
- 2) BP control
 - HTN and renal insufficiency more common in males
 - 60% of those that don't yet have renal insufficiency have HTN
- 3) renal insufficiency
 - ~2% chance of renal failure by age 40, ~25% by age 50, and ~50% chance by age 73
 - rate of renal deterioration correlates with rate of cyst growth
 - control of HTN can delay deterioration
 - dialysis, renal Tx
- 4) pain control
 - 50-70% will have loin or back pain from stones, infections, hemorrhage, etc
 - percutaneous aspiration + instillation of sclerosant
 - laparoscopic unroofing of cysts (Rovsing's procedure) } doesn't worsen renal fxn
 - Nx
- 5) treatment of infections
 - more common in women

Table 114-5 -- Comparison of Autosomal Recessive and Autosomal Dominant Polycystic Kidney Disease

Item	Autosomal Recessive Polycystic Kidney Disease (ARPKD)	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Gene defect	Chromosome 6	Chromosomes 4 and 16
Incidence	1:5,000 to 1:40,000	1:500 to 1:1,000
Usual age at clinical presentation	Perinatal	Third to fifth decades
Typical sonographic appearance of kidneys	Symmetrically enlarged, homogeneous, hyperechogenic kidneys	Large cystic kidneys, sometimes asymmetrical
Histology	Collecting duct ectasia; cysts derived principally from collecting duct	Microcysts and macrocysts derived from entire nephron
Liver	Always congenital hepatic fibrosis but of varying severity	Cysts, mostly in adults (on very rare occasions a newborn may have congenital hepatic fibrosis)
Other system involvement	None	Intracranial aneurysms; colonic diverticuli; mitral valve regurgitation; cysts of other organs

→ AR PCKD vs AD PCKD

JUVENILE NEPHRONOPHTHISIS / MEDULLARY CYSTIC DISEASE COMPLEX

List differences b/w Juvenile nephronophthisis & Medullary cystic disease complex (CHART)?

	Juvenile nephronophthisis	medullary cystic disease complex
Inheritance	→ AR (chromosome 2) - NPH1, NPH2, NPH3	→ AD (unknown chromosome) - MCKD1, MCKD2
Incidence	→ 1 in 50,000 births	→ 1 in 100,000 births
ESRD	→ most by early teens	→ usually by 20-40's
Medullary cysts	→ develop after renal failure - 40% develop cysts	→ may develop before onset of renal failure - 85% develop cysts
Tubular BM	→ thickened BM	→ may not be thickened
Symptoms	→ polyuria, polydipsia, anemia, growth retardation - onset usually after age 2 → no HTN (salt-wasting)	→ polyuria, polydipsia, anemia, and may have hematuria and proteinuria - onset after patient fully grown → HTN (no salt-wasting nephropathy)

What are the 3 main types of juvenile nephronophthisis?

- juvenile } NPH1 gene
- adolescent } NPH2 gene
- infertile } NPH3 gene

What are some anomalies that are associated with juvenile nephronophthisis?

- retinitis pigmentosa } 16%
- } called Senior-Loken syndrome if both conditions exist
- skeletal abN's
- hepatic fibrosis
- Bardet-Biedl syndrome } obesity, MR, polydactyly, retinitis pigmentosa, hypogenitalism

How do Juvenile nephronophthisis & medullary cystic disease complex appear on IVP?

- early stages } N or slightly shrunken kidney
- } homogeneous streaking of medulla (retention of contrast w/in dilated tubules)
- late stages } no value
- no calcifications

How do Juvenile nephronophthisis & Medullary cystic disease complex appear on U/S?

- parenchyma may look hyperechogenic due to tubulointerstitial fibrosis
- **kidney is N size early on then develops tubulointerstitial nephritis and atrophy starts, resulting in a small kidney with a granular surface**
- cysts may be seen at corticomedullary junction if large enough
 - cysts more common and seen earlier with medullary cystic disease complex
 - cysts are usually 1mm to 1cm

What is the management of Juvenile nephronophthisis & medullary cystic disease complex?

- early Na replacement (for juvenile nephronophthisis especially)
 - supportive therapy for renal failure until dialysis or renal Tx
- } no recurrence after Tx

CONGENITAL NEPHROSIS

What is congenital nephrosis?

- condition associated with “microcysts”
- dilatation of PCTs
- profound proteinuria

What are the 2 main types of congenital nephrosis?

- 1) Finnish type (CNF)
 - more common
 - **AR inheritance (chromosome 19)**
 - **associated with enormously enlarged & edematous placenta**
 - **accounts for 25% of birth weight**
 - presents early after birth
 - **get profound proteinuria } renal failure at birth**
 - edema & starvation from severe protein loss
 - see proliferation of mesangial cells on histology
 - interstitial fibrosis present
- 2) Diffuse mesangial sclerosis (DMS)
 - sporadic or familial
 - may be related to gene NPHS1 (encodes protein nephrin)
 - **N placenta**
 - **also get proteinuria } most get renal failure by age 3**
 - onset is slightly later with Dx usually made by 1 yr of age
 - see acid-Schiff +ve and silver phosphate-staining mesangial fibrils on histology
 - interstitial fibrosis present and more pronounced

What other condition is DMS congenital nephrosis associated with?

- **Denys-Drash syndrome** (nephrotic syndrome + Wilms' +/- male pseudohermaphroditism)
→ the nephropathy seen in Drash syndrome is actually DMS

How is the diagnosis of congenital nephrosis made?

- 1) prenatally
 - amniotic fluid
 - CNF type can be diagnosed by elevated amniotic AFP (from fetal proteinuria) as early as 6 weeks gestation
- 2) postnatally
 - U/S
 - shows enlarged kidneys that are more echogenic than liver or spleen
 - pyramids are small and hazy with absent CM junction

What is the management of congenital nephrosis?

- [illegible]

FAMILIAL HYPOPLASTIC GLOMERULOCYSTIC KIDNEY DISEASE (CORTICAL MICROCYSTIC DISEASE)

What is familial hypoplastic glomerulocystic kidney disease?

- AD inheritance
- **diagnosis requires 4 features**
 - 1) stable or progressive chronic renal failure
 - 2) small or N sized kidneys with irregular calyceal outlines and abN papillae
 - 3) present in 2 generations of a family
 - 4) histologic evidence of glomerular cysts
 - thin-walled and usually subcapsular
- may find marked prognathism in some patients

MULTIPLE MALFORMATION SYNDROMES WITH RENAL CYSTS

List common multiple malformations syndromes associated with renal cysts (CHART)?

→ **AD inheritance**

- 1) **Tuberous sclerosis** } **cysts are of variable sizes, eosinophilic, with hyperplastic lining**
 - } adenoma sebaceum, epilepsy, retardation, subependymal tubers, etc
 - } also get **AMLs (more common than cysts) and RCC (2%)**
- 2) **VHL disease** } **cysts are of variable size with hyperplastic lining**
 - } cerebellar hemangioblastomas, retinal angiomas, pheo's, pancreatic cysts, epididymal cystadenomas
 - } also get **clear cell RCC (35-40%)**

→ **AR inheritance**

- 1) **Meckel's syndrome** } large cysts with fibromuscular collars probably arising from collecting ducts
 - } microcephaly, polydactyly, posterior encephalocele
 - } also get **renal dysplasia & hypoplasia**
- 2) **Jeune's asphyxiating thoracic dystrophy** } **cysts range from subcapsular cortical microcysts to dysplasia with cystic components (similar to AD PCKD)**
 - } small chest and respiratory failure
 - } also get **renal dysplasia**
- 3) **Zellweger's cerebrohepatorenal syndrome** } **cysts vary from glomerular microcysts to 1cm cortical**
 - } hypotonia, high forehead, hepatomegaly
- 4) **Ivemark's syndrome** } **renal-hepatic-pancreatic dysplasia**

→ **X-linked dominant disorders**

- 1) **orofaciodigital syndrome** } **cysts develop with age**
 - } hypertrophic lingual & buccal frenula, cleft lip/palate/tongue

→ **chromosomal disorders**

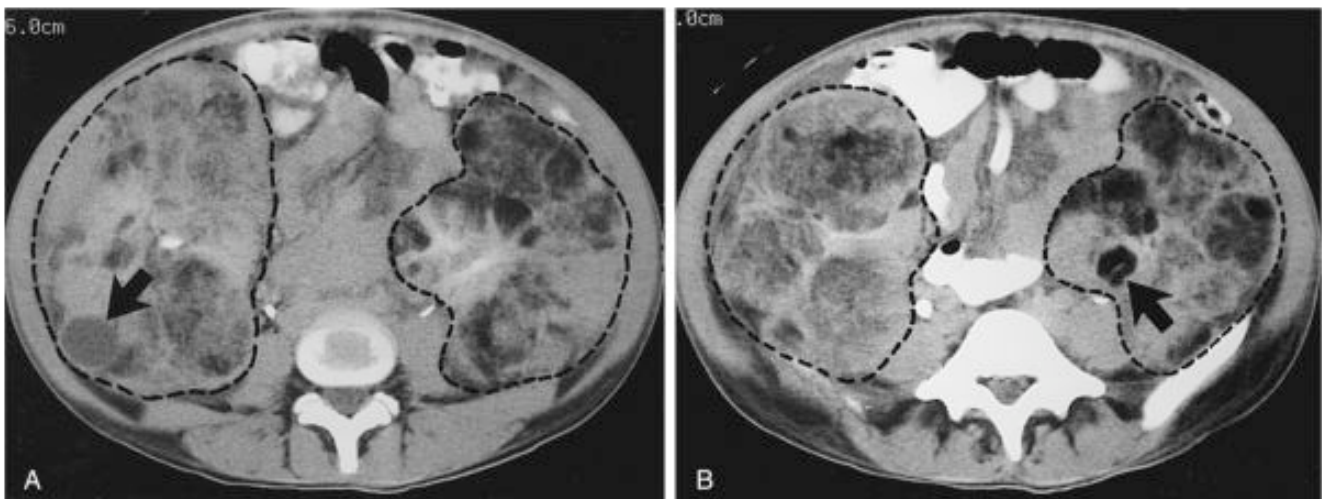
- 1) Trisomy 13 (Patau's) \
- 2) Trisomy 18 (Edwards') } **microscopic cysts**
- 3) Trisomy 21 (Down) /

What is the Tuberous Sclerosis complex?

- kidney have cysts, AMLs, or both } **AMLs more common (40-80%) than cysts (20%)**
 - classic triad of **epilepsy (80%) + mental retardation (60%) + adenoma sebaceum (75%)**
 - hallmark lesion of CNS is superficial **cortical hamartoma of cerebrum & calcified periventricular subependymal nodules**
 - **AD with variable penetrance**
 - **TSC1 (chromosome 9) encodes hamartin**
 - **TSC2 (chromosome 16) encodes tuberin**
 - may have overlap with AD PCKD (PKD1 gene on chromosome 16)
 - **variable sized cysts with hyperplastic lining**
 - **increased incidence of RCC (2%)** } **likely from hyperplastic lining**
- Rx → MR head + serial imaging of kidneys to assess AMLs

List common features of Tuberous Sclerosis.

- | | |
|-----------------------------|--|
| - mental retardation | - skin adenoma sebaceum (facial angiofibromas – reddish spots or bumps) |
| - renal cysts (35%) | - ungal or subungal (nails) fibromas |
| - renal AMLs (~50%) | - ash leaf spots (white spots) |
| - RCC (1-3%) | - Shagreen patches |
| - pheochromocytoma | - bone cysts |
| - epilepsy | - lung lymphangioleiomyomatosis (LAM) } almost exclusively in young females |
| - cortical tubers | - cardiac rhabdomyomas |
| - retinal hamartomas | |
| - subependymal nodules | |



→ TUBEROUS SCLEROSIS } enhanced CT showing renal cysts (arrow A) and AMLs (arrow B)

What is VHL disease?

- cysts are of variable size, often multiple and bilateral, with hyperplastic lining
→ 40-75% have cysts
 - VHL type 1 (RCC without pheo) and VHL type 2 (RCC + pheo)
→ type 3 also exists } pheo without RCC
→ **VHL has overall 50% incidence of clear cell RCC } 30% die from RCC**
 - AD inheritance
→ **chromosome 3p25**
→ VHL protein inactivates HIF, a regulator of VEGF, PDGF, etc
→ lack of VHL results in lack of ubiquitin-mediated HIF-1 α down-regulation
→ HIF-1 α is allowed to up-regulate VEGF, TGF α , PDGF, epo, CA-9, etc
 - **manifestations include (organs that tubularize by day 21):**
 - RCC (~50%) } most common cause of death from VHL
 - renal cysts (~40%)
 - benign retinal angiomas (~60%) } **earliest finding**
 - benign CNS hemangioblastomas (~60%) } usually cerebellar or spine
 } **most common finding**
 - pheochromocytomas (~20%)
 - pancreatic cysts (~45%)
 - pancreatic neuroendocrine tumours (islet cell)
 - epididymal cystadenomas (~20%)
 - endolymphatic sac tumours (~10%)
 - **>50% of deaths associated w/ CNS hemangioblastomas } now RCC is most common cause of death**
- Rx → screening CT every 1-2 yrs recommended
→ neuro Sx and ophtho consults
→ partial vs Radical Nx for RCCs } **nephron-sparing when possible**
→ screening only recommended for family with genetic evidence of the disease
- | | |
|-----------------|-----------------------------------|
| - retinal exams | \ done every 4yrs if normal but |
| - abdo CT | / every 2yrs if renal cysts found |

What are the NIH recommendations for VHL?

- 1) annual P/E and eye check starting as infant
- 2) periodic hearing test starting as infant
- 3) urinary catecholamines at 2yrs old then q1-2yrs
- 4) MRI of CNS q2yrs starting at age 11
- 5) abdo/pelvis U/S annually starting at age 11
→ CT q6/12 if cysts or tumours develop



→ VHL syndrome
- RCC (arrow), renal cysts, pancreatic cysts

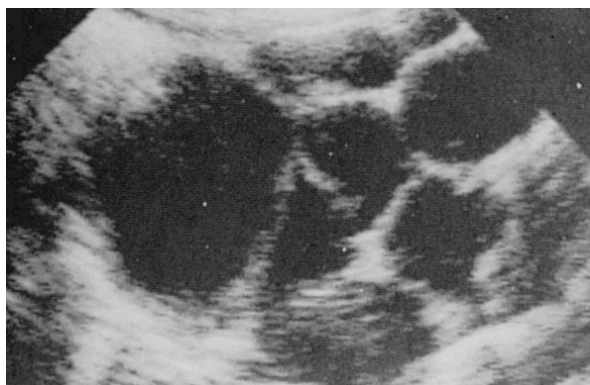
- **cysts** are lined with **low cuboidal epithelium**
- cysts separated by thin fibrous septa and primitive dysplastic elements (**primitive ducts**)
- often see **immature glomeruli**
- rarely see mature glomeruli

How do you differentiate MCDK from UPJO?

MCDK	UPJO
- non-reniform shape	- reniform shape
- random distribution of cysts of various sizes	- "cysts"/calyces found at periphery
- cysts of various sizes	- "cyst"/calyces all relatively similar in size
- no large central cyst	- pelvis represented by large central "cyst"
- no visible communication b/w cysts	- communication b/w "cysts"
- very small cysts present b/w cysts	- no small cysts b/w "cysts"
- no function on DMSA	- function seen on DMSA
- absent or small renal artery	- N renal artery
- may have hemitrigone or asymmetrical trigone	- N cysto

What is the work-up for suspected MCDK?

- 1) U/S } confirm normal contralateral kidney
 } to r/o severe hydronephrosis
 → MCDK usually has randomly distributed cysts and no large central cyst
 → MCDK has no visible communications between cysts
- 2) VCUG } r/o contralateral VUR
 → **routine VCUG controversial**
 → if N U/S may not need to do it } even if VUR present, likely it's mild & will resolve
- 3) renal scan (DMSA) } no functional renal tissue confirms MCDK



→ MCDK } U/S showing large cysts arranged in haphazard manner with no evidence of connections or the present of a large central/medial cyst

What is the management of MCDK?

- 1) assessment of contralateral kidney is essential } U/S +/- VCUG
- 2) no role for prophylactic removal } NO INCREASED RISK OF WILMS' TUMOUR
 → some would argue, there is a slightly higher risk
 } NO INCREASED RISK FOR HTN
 → Nx may not even cure HTN if present
- 3) f/u imaging of MCDK is controversial } how long do we follow???
 } how often do we image???

What are the indications to remove a MCDK?

- mass effect } compromising feeding or breathing
- chronic infection
- causal HTN
- worrisome features for Wilms'

BENIGN MULTILOCULAR CYST (CYSTIC NEPHROMA)

What is the spectrum of multilocular cystic lesions in kids?

- **there is no evidence that one lesion can convert to another**
- prognosis is better, even with the malignant lesions

benign multilocular cyst → multilocular cystic partially differentiated Wilms' → multilocular cyst w/ nodules of Wilms' → Cystic Wilms tumour

What is a benign multilocular cyst?

- benign, nondysplastic
- neoplastic lesion
- **Dx can only be made after surgical excision**

How do benign multilocular cysts of the kidney usually present?

- bimodal presentation
 - before age 4 } 2x more likely to be M
 - after 30yrs of age } 8x more likely to be F
- kids } asymptomatic mass is most common presentation
- adults } usually present with flank mass, abdo pain, or hematuria
- most often unilateral

What is the histopathologic findings of benign multilocular cysts of the kidney?

- **Dx only made by surgical excision**
- bulky cysts circumscribed by a thick capsule
- cysts lined by cuboidal or low columnar epithelial cells } **normal lining**
- septa are composed of fibrous tissue +/- well-differentiated tubules
 - no poorly differentiated tissues

What is the role of imaging for benign multilocular cysts of the kidney?

- U/S and CT can distinguish MCDK from benign multilocular cyst
 - however, neither study can reliably differentiate benign multilocular cyst from multilocular cyst w/ nodules of Wilms or adenocarcinoma, mesoblastic nephroma, cystic Wilms tumour, or clear cell sarcoma

What is the management of benign multilocular cyst?

- **Nephrectomy** } partial if well circumscribed & well-preserved normal tissue
 - more likely in adults
 - } radical Nx otherwise
 - esp. if suspicious for multilocular cyst w/ nodules of Wilms or cystic Wilms'
- **CHEMO** } if confirmed multilocular cyst w/ nodules of Wilms or cystic Wilms
 - better prognosis than usual Wilms'

What is Perlmann's syndrome?

- benign multilocular cystic lesion in adults

SIMPLE CYSTS

What are simple cysts?

- oval to round lesions with smooth outline } not connected to nephron
- cyst is bordered by a single layer of flattened cuboidal epithelium
- can be single or multiple, unilateral or bilateral
- rare in a fetus } most resolve by birth
- **uncommon in kids } incidence increases in adults as they age**
- usually incidental } can cause pain, hematuria, abdo mass and rarely HTN or obstruction

What are the histopathologic features of simple renal cysts?

- variable size } most are <2cm
- fibrous wall of varying thickness } no renal elements
- cyst lined by single layer of flattened **cuboidal epithelium**

What are the imaging modalities used to assess simple renal cysts?

- U/S } best imaging test for simple cysts
- if any abN features on U/S, perform CT scan or MRI
- if cysts are diffuse, multiple, or bilateral then need to r/o AD PCKD } screen family also

What are the U/S features used to make the diagnosis of a simple cyst?

- 1) sharply defined, thin distinct smooth wall
- 2) spherical or oval
- 3) good transmission of sound waves through cyst + acoustic enhancement behind cyst
- 4) no internal echoes

What are the CT features used to make the diagnosis of a simple cyst?

- 1) sharp, thin, distinct, smooth walls and margins
- 2) spherical or ovoid shape
- 3) homogeneous content
- 4) HU <20 } some benign cysts can be hyperdense (HU 20-90)

What is the Bosniak classification of renal cysts (CHART)?

- Bosniak I } simple cyst
Rx → no surgery (<5% risk of malignancy)
- Bosniak II } simple cyst + few thin septations, minimal calcification, or hyperdense (<3cm)
Rx → no surgery (15% risk of malignancy)
- Bosniak IIF } slightly thicker/more nodular cyst wall + minimal “perceived” septal enhancement
} hyperdense cyst >3cm
Rx → no surgery but serial imaging recommended
- Bosniak III } thick cyst wall + prominent septations + more calcifications + wall enhancement
Rx → surgical removal (50% risk of malignancy)
- Bosniak IV } irregular margins + SOLID vascular enhancing elements
Rx → surgical removal (85% risk of being cystic RCC)

What is the management of simple cysts?

- if asymptomatic (most) then can be left alone
- surgical management indicated only if symptomatic } pain, HTN, obstruction, infection
 - perc aspiration
 - perc aspiration + injection of sclerosant (Bismuth phosphate, ethanol, contrast)
 - intrarenal marsupialization
 - lap unroofing of cyst

What are the indications for cyst puncture?

- 1) suspected infection
- 2) low-level echoes on U/S but classic cyst on CT
- 3) borderline lesion in poor surgical candidate

What variations of simple cysts exist?

- 1) unilateral renal cystic disease
 - simple cysts of varying size found side by side } usually large
 - often more numerous at one pole
 - variation of simple cysts
 - rare } more likely to be unilateral asymmetric AD PCKD

Rx → need long-term f/u to r/o development of cysts in other kidney } AD PCKD
→ may need to r/o other conditions such as VHL & tuberous sclerosis
- 2) autosomal dominant simple cyst disease
 - familial syndrome of simple cysts
 - no evidence of AD PCKD, VHL, tuberous sclerosis, etc

MEDULLARY SPONGE KIDNEY (MSK)

What is MSK?

- **dilatation of distal collecting ducts + small renal cysts (medullary) + diverticula**
 - cysts lined by urothelium
 - dilated ducts have appearance of bristles on a brush
- **can also have ectatic ducts that are filled with calcifications**
 - **medullary nephrocalcinosis**
 - “bouquet of flowers” appearance
- **non-heritable condition**
- **75% bilateral**
- more common in stone formers } especially F stone formers
- also more common in F with UTIs

List anomalies that are associated with MSK. (“BECH”)

- **Beckwith-Wiedemann syndrome**
- **Ehlers-Danlos syndrome**
- **Caroli’s disease**
- **hemihypertrophy**

What is Beckwith-Wiedemann syndrome?

- most cases are sporadic but 15% are genetic (AD inheritance)
- features include macroglossia, hemihypertrophy, organomegaly (kidney, liver), adrenal Ca, Wilms’ tumour, medullary renal cysts, hypoglycemia from pancreatic β cell hyperplasia, MSK

How does MSK usually present?

- many are asymptomatic
- **renal colic (50%)**
- **hypercalciuria (30-50%)** } most common metabolic derangement
- UTIs (20-30%)
- gross hematuria (10-20%)
- hypocitraturia
- impaired concentrating ability

What are the cause of nephrocalcinosis?

→ CORTICAL (uncommon)

- Cortical necrosis (acute)
- primary **O**xalosis
- chronic **R**ejection
- **T**oxins (ethylene glycol, etc)
- **I**nsufficiency of pyridoxine (B6)
- **C**hronic GN
- **A**lport's syndrome
- sick **L**e cell disease

→ MEDULLARY

- **type 1 distal RTA (2nd most common)**
- **MSK (common)**
- sarcoidosis
- excess vitamin D
- renal TB
- renal papillary necrosis
- Dent's disease
- Paget's disease
- other causes of hypercalcemia
 - **1° hyperPTH (most common)**
 - immobilization
 - malignancy
 - hyperT4
 - pheochromocytoma
 - milk-alkali syndrome
 - Vitamin A, Vitamin D
 - meds (steroids, HCTZ, Li, E)

What are the IVP findings suggestive of MSK?

- 1) enlarged kidneys + medullary nephrocalcinosis } bouquet of flowers
 } bristles on a brush
- 2) elongated papillary tubules with puddling of contrast
- 3) papillary contrast blush + persistent medullary opacification



→ MEDULLARY SPONGE KIDNEY } IVP

- } puddling of contrast in ectatic papillary collecting ducts
- } enlarged kidneys

What is the management of MSK?

- treatment of complications of MSK
 - stones (Ca oxalate most common)
 - UTIs } more common in stone formers
- thiazides } if stones or if hypercalciuria
- inorganic phosphates } if thiazides not effective
 - } avoid in patients with UTIs
 - risk of struvite stones
- consider prophylactic Abx for those with recurrent UTIs
- SWL and PNL for stones

SPORADIC GLOMERULOCYSTIC KIDNEY DISEASE

What is sporadic glomerulocystic kidney disease?

- cysts of the glomeruli or Bowman's space that are present diffusely and bilaterally
- Dx made only if
 - 1) non-heritable condition (no family members)**
 - 2) bilaterally enlarged kidneys with small cysts, mainly of Bowman's space**
 - 3) no associated anomalies**
- may be hard to differentiate from AD PCKD } could be a new variant of classic AD PCKD
- different from familial hypoplastic glomerulocystic kidney disease } AD inheritance
 - } small or N sized kidneys

What conditions are associated with glomerular cysts (CHART)?

- [illegible]

ACQUIRED RENAL CYSTIC DISEASE

What is acquired renal cystic disease?

- cystic disease that develops in ESRD } **not only associated with hemodialysis**
 } incidence increases with time
 } more common in ESRD from nephrosclerosis (HTN)
- **Dx made once at least 3-5 cysts seen on imaging**
- can also get development of adenomas
- 7x more common in M and usually more advanced
- more common in Blacks & Japanese
- may cause pain & hematuria & infection
- **associated with ↑'d risk of RCC (usually papillary)**

What is different about RCC associated with ARCD?

- 1) approximately **5x more common** (10x in Blacks) than general population
- 2) age at occurrence is **~5yrs younger cf general population**
- 3) **even more common in M** (7x vs only 2x more common in general population)
- 4) usually **multiple & bilateral** } if RCC doesn't develop after ~10yrs, likely won't develop

What is the cause of ARCD?

→ several theories

- 1) uremic toxins
 - lesions are multiple and bilateral
 - regression of cysts seen after renal Tx
 - return of cysts after failed Tx and resumption of dialysis
- 2) loss of functioning renal tissue leads to production of renotropic agents that induce tumours

How does ARCD usually present?

- **most common } flank pain + hematuria**
- bleeding seen in ~50% } urine or retroperitoneum
- polycythemia } may have increased epo production

What are the histologic findings of ARCD?

- cysts are mainly in cortex } microcysts
- cysts are usually 0.5 to 1.0cm
- can be filled with Ca oxalate crystals
- most cysts are lined by flat epithelium
 - **can see hyperplastic lining in some cysts } explains RCC**
- adenomas

What other types of cysts are associated with hyperplastic lining?

- ARCD \ increased risk of RCC
- VHL renal cysts /
- TS renal cysts } likely higher risk of RCC
- AD PCKD } NO higher risk

What is the best imaging modality to assess ARCD?

- CT or MRI } better than U/S

What is the management of ARCD?

→ treatment

- embolization or Nx } if symptomatic (hematuria, loin pain, etc)
- percutaneous drainage of infected cysts } Nx if not effective
- radical Nx } evidence of RCC

→ screening

- routine screening recommended if risk factors } prolonged dialysis, M gender
- **cysts may resolve w/ renal Tx but risk of RCC does not seem to decrease after Tx**

CALYCEAL DIVERTICULUM (PYELOGENIC CYST)

→ smoothly outlined, intrarenal sac that communicates with the pelvicalyceal system by a narrow neck

→ **lined by transitional epithelium**

PARAPELVIC AND RENAL SINUS CYSTS

What is the difference between parapelvic cysts & renal sinus cysts?

- parapelvic cysts } cysts arising from renal parenchyma that happen to abut renal pelvis
- renal sinus cysts } cyst derived from arteries, lymphatics, or fat within renal sinus (NOT kidney)

What is a renal sinus cyst?

- derived from tissue within renal sinus } **lymphatic origin is most common**
- **usually multiple & bilateral** } can have “polycystic disease of the renal sinus”
 - multiple renal sinus cysts, stretching of infundibula, and medial displacement of pelvis
- most appear after 5th decade
- may be associated with inflammation, obstruction, or a stones

Chapter #115 – Anomalies and Surgery of the UPJ in Children

EVIDENCE

What is the bimodal presentation of UPJO?

- 1) neonatal period } due to detection of antenatal hydro (**most cases found in peri-natal period**)
 - 2) adolescence } due to symptomatic occurrences
- **most common cause of UNILATERAL hydro in fetal kidney (~50%)**
- more common in M } **L side more common (67%)**
- bilateral UPJO occurs in ~10% of cases } both synchronous and asynchronous

ETIOLOGY

What are the causes of UPJ obstruction?

→ intrinsic } narrowing with interruption in development of circular musculature of UPJ or an alteration in collagen fibers in and around the muscular cells

→ extrinsic } more often symptomatic

1) congenital

→ intrinsic

- aperistaltic segment of ureter } N spiral smooth muscle replaced by abN longitudinal muscle bundles or fibrous tissue
- true congenital stricture } excess collagen deposition
- congenital kinks or valvular mucosal folds } mucosa & smooth muscle
 - Ostling's folds (valvular mucosal folds) are due to differential growth rates of ureter and body of child (**not obstructive ... disappear w/ linear growth**)

→ extrinsic

- crossing vessels } LP vessel (truly aberrant if crosses ureter **anteriorly**)
- external bands or adhesions
- persistent fetal convolutions

2) acquired

- stone disease
- post-op iatrogenic scarring/ischemia
- inflammatory stricture (eg RPF)
- urothelial malignancy
- benign upper ureteral fibroepithelial polyps
- VUR

3) idiopathic

What is lower pole UPJO?

- **occurs in kidneys with an associated incomplete renal duplication**
 - incomplete duplications are found in 70%, compared to complete duplications (30%)
- **hydronephrosis of LP moiety**
- due to short bifurcating ureteral segment distal to the UPJ or a longer bifurcating ureteral segment
 - short segment Rx'd by excision of stenotic ureteral bifurcation + end-to-side pyeloureterostomy
 - long segment best treated by a typical dismembered pyeloplasty

List anomalies associated with UPJO

→ associated GU anomalies found in ~50% of infants

- **contralateral UPJO (10-40%)** } **most common contralateral anomaly (ie B/L UPJO)**
 - contralateral renal dysplasia
 - contralateral MCDK
 - unilateral renal agenesis (5%)
 - duplicated collecting system } **UPJO usually occurs in LP moiety**
 - horseshoe kidney
 - ectopic kidney
 - **VUR found in 20-40%** } usually low grade
- VACTERL syndrome } UPJO found in ~10-20%

SYMPTOMS/PRESENTATION

How does UPJO usually present?

- **infants** } **usually asymptomatic**
 - can present w/ FTT, feeding difficulties, sepsis from infection, or hematuria from stones
 - } antenatal U/S (CURRENT) VS palpable abdominal mass (HISTORIC)
- **adolescents** } **usually symptomatic**
 - } UTI (30%)
 - } episodic flank or upper abdo pain +/- N/V
 - often exacerbated by diuresis (Dietl's crisis)
 - } hematuria (25%) from rupture of mucosal vessels in dilated collecting system
 - } HTN

What is the Society of Fetal Urology (SFU) grading system of hydronephrosis?

- grade 1 } slight splitting
 - slightly dilated renal pelvis WITHOUT caliectasis
 - grade 2 } pelviectasis
 - moderately dilated renal pelvis with MILD caliectasis
 - grade 3 } pelviectasis + caliectasis
 - large renal pelvis w/ dilated calyces & N renal parenchyma
 - grade 4 } severe pelvicaliectasis + thinning of renal parenchyma
 - thinning >50% of contralateral kidney
- others have broken down grade 4 into 4a (segmental thinning) vs 4b (diffuse thinning)
- limitation } can't discern grade 3 from grade 4 if single kidney

What other methods have been used to assess antenatal hydronephrosis?

- 1) Anterior-Posterior Diameter of renal pelvis (APD)
 - mild is ≤9 mm
 - moderate is 9-15 mm
 - severe is ≥15 mm

} numbers depend on trimester & different cut-offs
/ have been used by different groups
- 2) Renal parenchymal-pelvic area ratio
 - ratio <1.6 correlates well with obstruction } can predict the need for Sx

DDx of unilateral antenatal hydronephrosis?

- **UPJO (most common → ~50%)**
- VUR
- UVJO
- dilatation of one unit of duplex kidney
- MCDK
- PUVs
- megaureter

DDx of bilateral antenatal hydronephrosis?

- transient physiologic hydro (most common)
- **bilateral VUR**
- PUVs
- bilateral UPJO
- bilateral primary megaureter
- PBS (VUR)
- bilateral duplication w/ obstruction
- prolapsing ectopic ureterocele (BOO)

DIAGNOSIS

When is the initial post-natal U/S performed for suspected UPJO?

- **w/in 48hrs of life if severe B/L antenatal hydro & concerned about PUV**
→ VCUG within 1st week if severe B/L hydro, otherwise 1 month
- **at 1month if unilateral severe antenatal hydronephrosis**
→ VCUG at 1-2 months if hydro persists
- absence of hydroureter makes UPJO more likely

What imaging studies are used to help make the Dx of UPJO?

→ **all modalities are imprecise and there is no definitive gold standard to Dx UPJO**

1) U/S

- size of renal pelvis (AP diameter) can be correlated with likelihood of obstruction
→ can't confirm Dx and also can't predict prognosis, especially in newborns
- **renal parenchyma-pelvic area ratio** to improve diagnostic accuracy of U/S
→ **ratio <1.6 correlates with significant obstruction**
- sequential U/S studies are beneficial because they can define a trend
→ can also look for **compensatory growth of N contralateral kidney**
- measuring RI's via renal duplex Doppler U/S can also delineate obstruction
→ **elevated RI's associated w/ obstructive pattern seen on renal scans (>0.75)**
→ adding lasix further accentuates difference b/w obstructed & non-obstructed

2) radionuclide renal scan

→ **differential function is most important variable of renal scans, not $T_{1/2}$**

- has largely replaced IVP
→ IVP still indicated when intermittent UPJO occurs
→ IVP easier to perform than renal scan when patient becomes symptomatic
- **“well-tempered” renogram is best study to define UPJO**
→ MAG3 preferred over DTPA in immature kidney
→ prehydration with 10-15cc/kg of NS + catheter placed just prior to study
→ diuretic injection } no correct time for diuretic (F -15, F 0, F +20)
→ **$T_{1/2} >20$ mins signifies obstruction and $T_{1/2} <10$ mins is non-obstructed**
- kidney with antenatal unilateral hydro that shows stable differential function & stable renal pelvic diameter is by definition NOT obstructed
- can't just look at slope of drainage curve either
→ simply having impaired drainage can't be used as a definition of obstruction in an asymptomatic infant with prenatal hydro
- must ensure empty bladder and allow gravity to have its full effect

3) MRI (investigational)

- dynamic contrast enhanced MRI is superior to U/S and renal scans
- excellent anatomic detail
→ better than U/S and renal scans } need to be hydrated to see collecting system
- can assess **differential renal fxn by calculating volume of enhancing parenchyma**
→ comparable to renal scans
- more specific than renal scans at defining obstruction
- further refinements include the **calculation of renal transit time (RTT)**
→ correlates with $T_{1/2}$ after diuretic challenge
→ complements determination of differential renal function
→ not as accurate if poor quality of functioning renal tissue

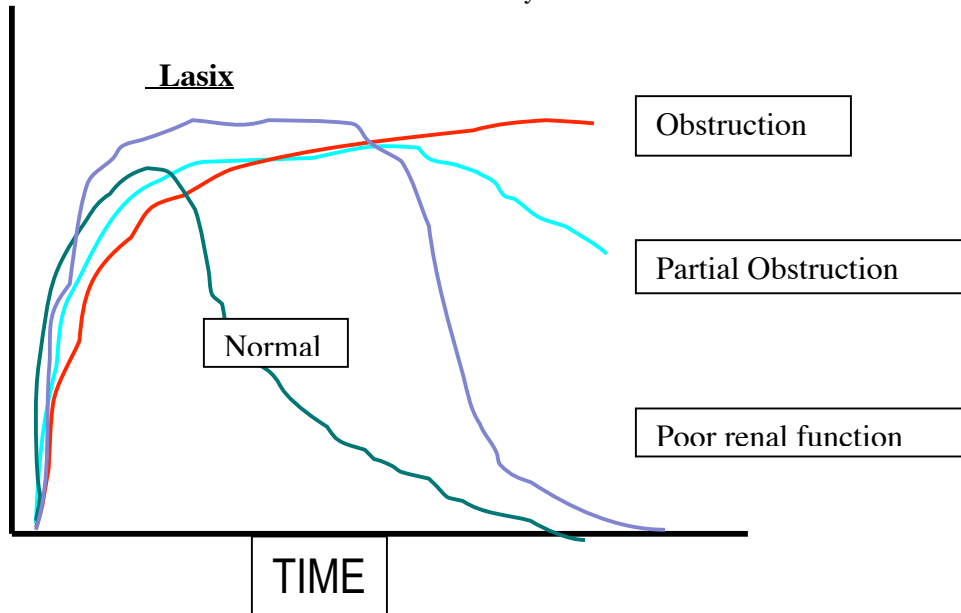
4) pressure-flow studies

- Whitaker test not usually performed in kids (>22cm H₂O is obstruction, N is <15cm H₂O)
- can measure pressure decay curves to try to delineate obstruction } still need NT
- pressure decay $T_{1/2}$ reflects efficient urine transport & relative compliance & volume of system
- **renal pelvic pressure >14 cm H₂O + a slow pressure decay suggests obstruction**

What is the role of nuclear renal scans in diagnosing obstructive uropathy?

- non-invasive, no contrast, no radiation
- radioactive tracers are given iv and used to evaluate functional info
 - tubular tracers (MAG3, hippurate) VS glomerular tracers (DTPA)
- $T_{1/2} < 10$ minutes = **normal**
- $T_{1/2} > 20$ minutes = **obstruction**
- $T_{1/2}$ 10-20 minutes = **indeterminate**
- give lasix to produce high-flow and r/o dilated but unobstructed system
 - standard is F+20 study
 - if equivocal, do a F-15 study } normalizes partially obstructed-looking curve
 - need to adjust lasix dose to renal function
 - empty bladder prior to renal scan (Foley if can't void)

What do the nuclear scan curves of an obstructed system look like?



Why is a MAG3 renal scan preferred over a DTPA renal scan in the pediatric population?

- **DTPA** } ~100% filtration >> “glomerular tracer”
 - **good to measure GFR & obstruction**
 - } 20% extraction coefficient in mature kidney
 - **not as good when kidney function is low or immature**
- **MAG3** } ~100% tubular secretion (in PCT) >> “tubular tracer” (some say 20% filtration)
 - better image quality, more accurate numerical values } **obstruction & GFR**
 - **can estimate RPF**
 - } higher extraction fraction (50% in mature kidney) with little cortical retention
 - **more accurate when kidney function is poor or immature**
- **DMSA** } 65% secretion + 35% filtration >> “cortical-tubular tracer”
 - **good for assessing parenchyma (scars) & split function**
 - gives information on GFR
 - **no good for UPJO as doesn't give info on drainage** } + cortical retention

What are the 3 phases of a normal renal scan?

- 1) uptake } slope depends on differential function
 - } eg poorly functioning kidney takes longer to uptake tracer (gradual slope)
- 2) peak } depends on combination of pelvic volume and timing of diuretic challenge
 - } eg large renal pelvis + late diuretic challenge means longer time to reach peak
- 3) falling phase } depends on many factors, not just presence of obstruction

What are the causes of a falsely delayed renal scan?

- capacious collecting system
- renal immaturity in neonates
- renal insufficiency
- dehydration
- presence of VUR
- ↑'d intravesical pressure (eg full bladder, neurogenic bladder)
- patient motion

What biochemical markers have been used to indicate renal tubular damage due to obstruction?

- 1) N-acetyl-β-D-glucosaminidase (NAG)
→ NAG levels elevated in UPJO if urine obtained from kidney (bladder urine can't discriminate)
- 2) TGF-β1
→ levels in renal pelvis & bladder elevated in UPJO

SURGICAL REPAIR

What are the indications for intervention in UPJO? } "BRUSSSHH"

- **Bilateral disease**
- **Renal function impairment** } overall (<40% w/ poor washout) OR ↓'ing on serial studies
- **UTIs**
- **Solitary kidney**
- **Symptoms**
- **Stones**
- ↑'ing **Hydronephrosis** on serial studies (eg APD >50mm)
- **HTN** (causal)

List factors that have been used to predict the need for surgical correction of UPJO in kids?

- 1) pre-natal APD ≥15-20mm
- 2) post-natal ipsilateral differential function ≤40%
- 3) symptomatic presentation
- 4) palpable hydronephrosis

What are the different types of open pyeloplasty techniques used for UPJO in kids?

- 1) dismembered pyeloplasty (Anderson-Hynes)
 - **GOOD for redundant pelvis, tortuous proximal ureter, high inserting ureter, & crossing vessel**
 - **NOT GOOD for long or multiple proximal strictures or if small, intrarenal pelvis**
→ Culp-DeWeerd Spiral preferred for long proximal ureteric strictures
- 2) Flap procedures
 - a) Foley YV-plasty
 - **GOOD for high inserting ureter** } largely replaced by Anderson-Hynes
 - **NOT GOOD for crossing vessel and redundant renal pelvis**
 - b) Culp-DeWeerd Spiral flap
 - **GOOD for redundant pelvis & if long proximal ureteric stricture**
 - **NOT GOOD for crossing vessel, small intrarenal pelvis, or high inserting ureter**
 - c) Scardino-Prince Vertical flap
 - **GOOD for large square redundant pelvis or moderately long proximal ureteric strictures**
 - **NOT GOOD if crossing vessel, small intrarenal pelvis, high inserting ureter**
- 3) Davis intubated ureterotomy
 - **GOOD for multiple or long proximal ureteric strictures** } **Culp-DeWeerd Spiral preferred**
- 4) ureterocalycostomy
 - **GOOD for small intrarenal pelvis, crossing vessel, associated renal anomalies (eg horseshoe), & failed pyeloplasty**
- 5) Fenger-plasty (Heineke-Mikulicz of UPJ)
- 6) Hellstrom procedures (angiopexy)

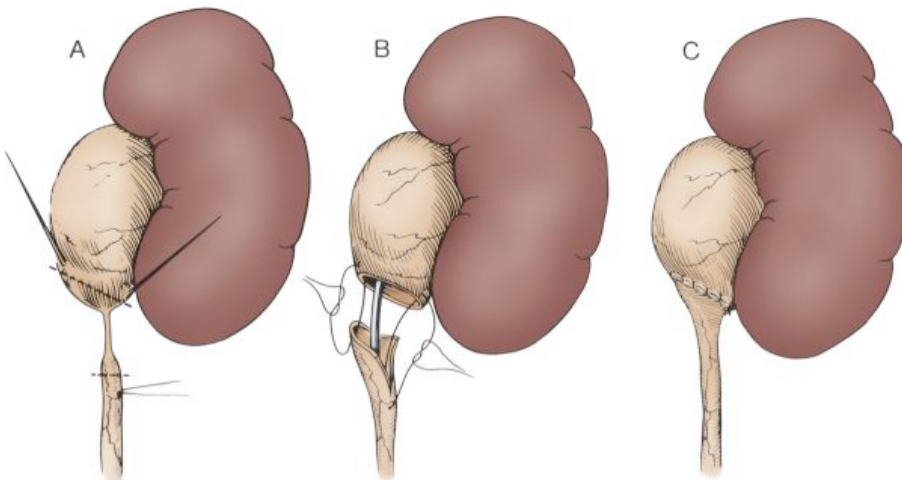
Why is the dismembered pyeloplasty universally so well accepted?

→ initially described by Anderson & Hynes '49 for retrocaval ureter

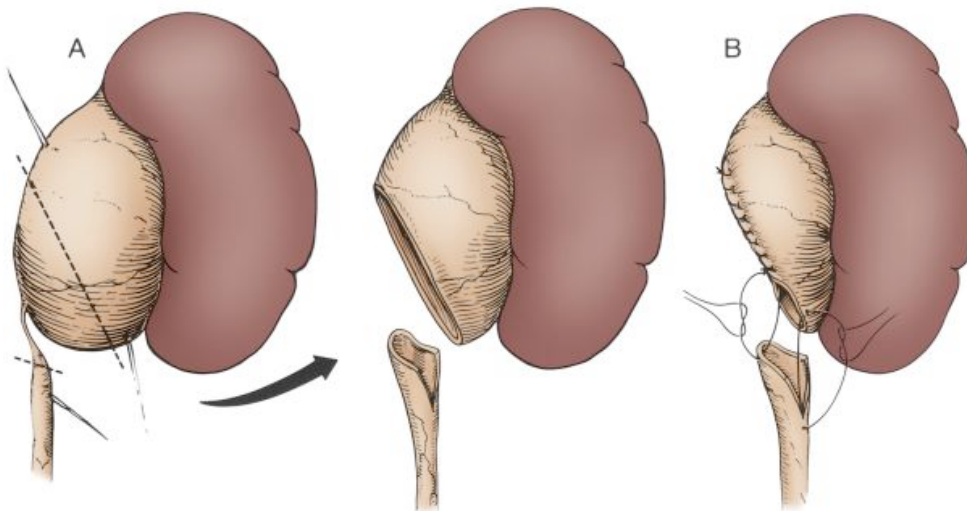
- 1) broad applicability } including preservation of anomalous vessels
- 2) excision of pathologic UPJ & appropriate repositioning
- 3) successful reduction pyeloplasty
- 4) easy to perform with several different approaches } ant. subcostal, flank, post. lumbotomy

What is the role of retrograde pyelography prior to UPJO management?

- anatomic detail of UPJO can be garnered from IVP
→ but now most do renal scans
- retrograde pyelogram performed at time of pyeloplasty will help surgeon decide type of pyeloplasty best suited for UPJO repair



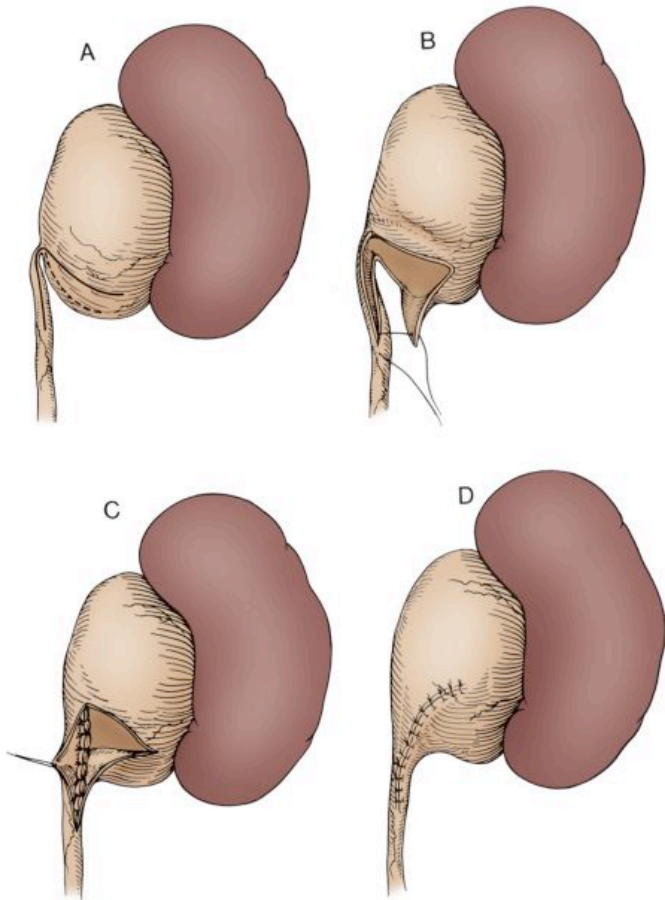
→ DISMEMBERED PYELOPLASTY (ANDERSON-HYNES)



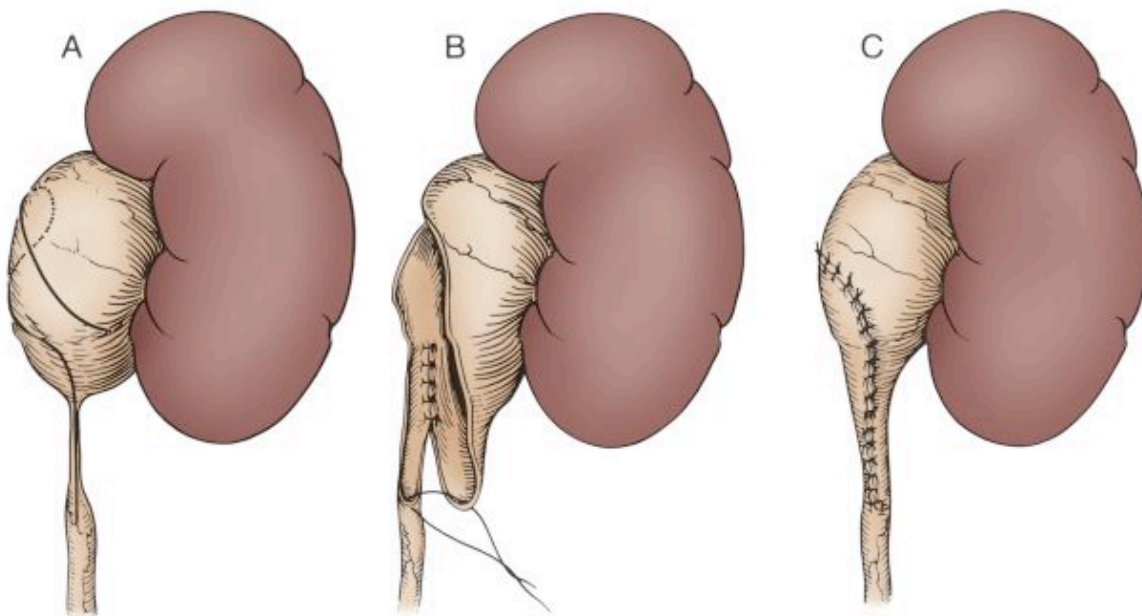
→ REDUCTION DISMEMBERED PYELOPLASTY (ANDERSON-HYNES)

Describe an Anderson-Hynes Dismembered Pyeloplasty.

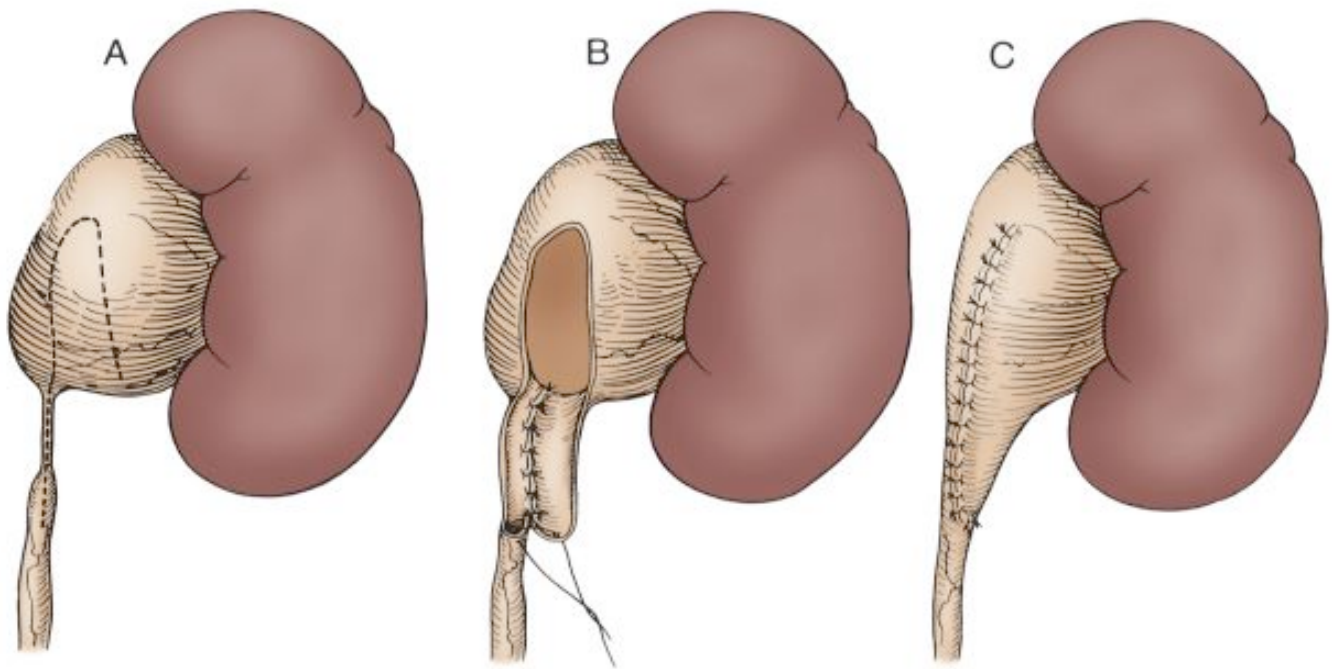
1. The anterior subcostal incision is a muscle-splitting incision that is made with the patient supine and a roll placed transversely beneath the patient to elevate the flank (Fig. 115-16).
2. Each muscle layer encountered is split in the direction of the muscle fibers until Gerota's fascia is identified by sweeping the peritoneum medially. The fascia is then incised posteriorly over the lateral aspect of the kidney.
3. The renal pelvis is identified by medial retraction of the peritoneum and lateral traction of the kidney. If the renal pelvis is significantly dilated, an Angiocath can be inserted to decompress the pelvis and facilitate identification of the UPJ.
4. Anterior exposure is usually better when a dismembered pyeloplasty is being performed. **Once the ureter and UPJ are identified, a traction suture is displaced anteriorly through the proximal ureter to minimize subsequent handling.**
5. The area of UPJ is dissected free to allow a clear area in which to perform the anastomosis. Traction sutures of 6-0 Prolene may be placed in the renal pelvis superiorly, medially, laterally, and inferiorly to the UPJ. When adequate ureteral length is confirmed and the pathology of UPJ identified, the ureter can be transected at the UPJ. If the ureter is short, the kidney is completely mobilized to determine whether it can be brought down sufficiently to allow a primary tension-free anastomosis.
6. After transection of the UPJ, the renal pelvis may not spontaneously drain until it is incised. This should be done after the site for anastomosis is chosen.
7. The ureter is **spatulated on the side opposite to the traction suture** using Potts tenotomy scissors. The distance over which the ureter is opened is variable, until healthy ureter is encountered, which springs open when forceps are placed into it.
8. The **portion of pelvis is excised**, usually a diamond-shaped segment that is present within the traction sutures that were placed in the renal pelvis. It is better to leave too much renal pelvis than too little, especially when resecting along the medial aspect of the renal pelvis. Infundibula can be encountered if one is not careful (Fig. 115-17).
9. The ureter and renal pelvis are aligned to ensure that the anastomosis can be accomplished without tension. If a nephrostomy tube is to be used, it is placed at this time. An inferior calix is chosen, preferably where the overlying parenchyma is not too thick. A Malecot catheter works well and is positioned away from the repair to minimize the chance of the catheter's causing urinary blockage through the reconstructed UPJ.
10. The anastomosis is started by placing the first 7-0 Maxon (Davis and Geck) suture at the apex of the "V" in the ureter and into the tip of the inferior pelvic flap. As the suture is tied down, the ureter and renal pelvis are brought together to minimize tension on the repair. A small feeding tube is placed into the ureter; it can be used to stabilize the ureter during the anastomosis. **A "no-touch" technique is employed with the ureter to minimize trauma** and edema to the ureteral tissue. Either interrupted sutures or a running closure may be used, depending on the surgeon's preference. The area of the initial anastomosis is critical to ensuring a watertight closure.
11. Before the repair is completed, the renal pelvis is irrigated to remove any blood clots or debris that could obstruct the UPJ. If an indwelling JJ ureteral stent is employed, it should be placed now, with care taken to place the stent into the bladder and renal pelvis without kinking it.
12. A Penrose drain is placed adjacent to the repair and brought out through a separate stab wound.
13. The kidney is returned to its native position, and perinephric fat, if available, is placed over the anastomosis.
14. Closure of the three fascia is readily accomplished, followed by closure of Scarpa's fascia and subcuticular skin.
15. A Foley catheter, which was placed at the beginning of the procedure, may be left in place for 24 to 48 hours postoperatively. The Penrose drain usually can be removed before discharge or, if left in place, it can easily be removed in the office 7 to 10 days postoperatively.



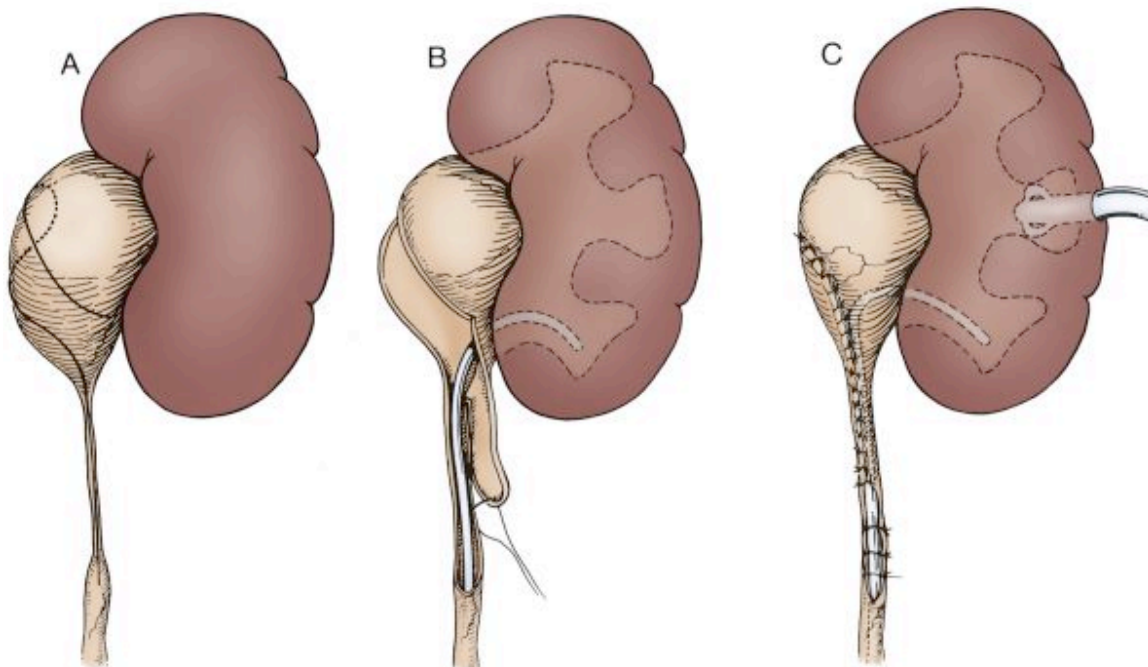
→ FOLEY YV-PLASTY



→ CULP-DeWEERD SPIRAL FLAP



→ SCARDINO-PRINCE VERTICAL FLAP



→ DAVIS INTUBATED URETEROTOMY

Describe a posterior lumbotomy approach to a dismembered pyeloplasty?

- patient placed in prone position with a roll under chest, pelvis, and knees
- skin incised and Scarpa's fascia sharply opened to expose lumbodorsal fascia
- vertical incision made in posterior lamella of lumbodorsal fascia
- lateral edge of lumbodorsal fascia is elevated
- sacrospinalis muscle is medially retracted
- incision is made through middle and anterior lamella of lumbodorsal fascia
 - watch for iliohypogastric nerve
- retract quadratus lumborum to expose Gerota's fascia beneath the paranephric fat
- open Gerota's fascia to expose renal pelvis
- place several holding sutures into renal pelvis
- identify ureter and place another holding suture into the ureter
- proceed with pyeloplasty

Describe a flank approach to a dismembered pyeloplasty?

- patient placed in lateral decubitus position and table flexed
- skin incision made off tip of 12th rib or, if necessary, a supracostal 12th rib incision is made
- divide external oblique and latissimus dorsi muscles
- divide internal oblique and serratus posterior inferior muscles
 - transversalis is a very thin layer and can be divided by hand
- peritoneum retracted medially
- Gerota's fascia opened longitudinally to expose perinephric space
- identify renal pelvis and ureter
- proceed with pyeloplasty

What are the minimally invasive approaches to UPJO repair?

- 1) endoscopic
 - antegrade vs retrograde
 - Acucise vs balloon dilation
 - endopyelotomy } cold knife, electrocautery, laser
 - always cut laterally
 - **good in slightly older kids**
 - **poor outcomes if crossing vessel**
 - **good after failed pyeloplasty } ureter is in dependent position**
 - ~80% success rate
- 2) laparoscopic
 - transperitoneal vs retroperitoneal } retroperitoneal approach slightly more difficult due to confined space for suturing, etc
 - **benefit not as substantial in very young kids (<2yrs) } less space for suturing**
 - success rate >95%
- 3) robot-assisted
 - transperitoneal vs retroperitoneal
 - new and promising

What are the different approaches to the kidney for laparoscopic pyeloplasty?

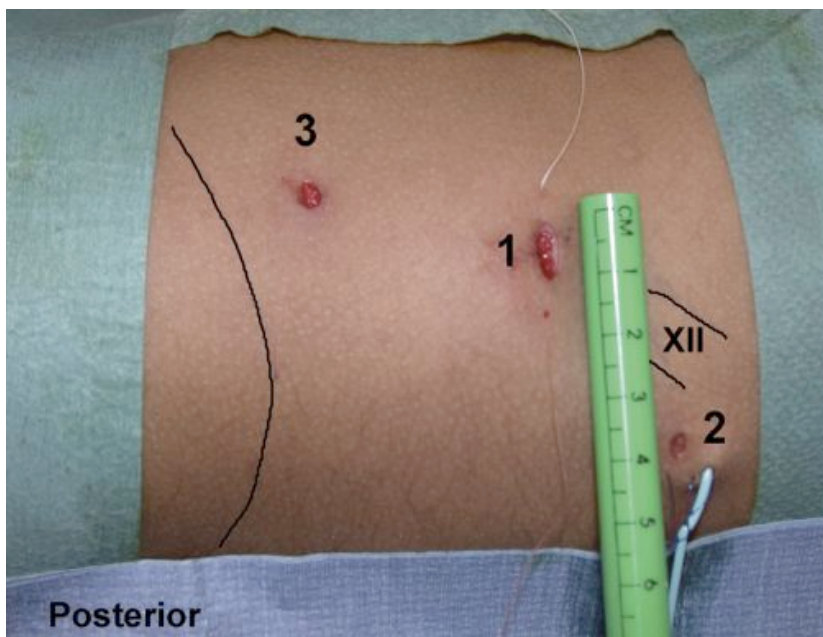
- retroperitoneal
 - 1) lateral } easier in young kids with less fat
 - 2) prone posterior
- transperitoneal
 - 1) flank
 - 2) supine

List advantages & disadvantages of retroperitoneal laparoscopic pyeloplasty.

- advantages
 - } lack of adhesions if prior abdo sx
 - } direct access to renal pelvis/hilum
 - } less post-op ileus,
 - } less risk of trocar site hernias
 - } less risk of peritoneal contamination (eg urine, infection, etc)
 - } less post-op shoulder tip pain
- disadvantages
 - } technically challenging (suturing is difficult)
 - } limited working space
 - } less familiar approach
 - } more lung complications (eg pneumothorax)

Describe gaining lateral retroperitoneal access for a Lap Pyeloplasty.

The patient is placed laterally, with sufficient flexion of the operating table to expose the area of trocar placement, between the last rib and the iliac crest (Fig. 115-20). In infants and younger children (under 6 years), our preference is to use lumbar padding to flex the patient laterally without flexing the operating table. Yeung and colleagues (2001) used different positioning based upon the kidney requiring surgery; semiprone for the right side and semilateral for the left side. Retroperitoneal access is achieved through the first incision, 15 to 20 mm in length, and one finger width from the lower border of the tip of the 12th rib (Fig. 115-21). The use of narrow retractors with long blades allows a deep dissection with short incision. Gerota's fascia is approached by a muscle splitting blunt dissection, opening under direct vision and placing the first blunt trocar (3 or 5 mm) directly inside Gerota's fascia. A working space is created by gas insufflation dissection, and the first trocar is fixed with a purse-string suture that is applied around the deep fascia to ensure an airtight seal and yet allow traction on the main trocar if needed to increase the working space. This type of fixation is preferable to the single-use self-retaining trocars, which are larger and interfere with the mobility of instruments. A second trocar (3 mm) is inserted posteriorly in the costovertebral angle, in front of the lumbosacral muscle. A third trocar (3 mm) is inserted in the anterior axillary line, a finger width from the top of the iliac crest. To avoid transperitoneal insertion of this trocar, the working space is fully developed and the deep surface of the anterior wall muscles is identified before the trocar is inserted. Insufflation pressure does not exceed 12 mm Hg, and the CO₂ flow rate is progressively increased from 1 to 3 L/min. Access to the retroperitoneum and creation of the working space are the keys to success in retroperitoneal renal surgery. Age is not a limiting factor for this approach. Young children have less fat and the access is easier. This approach has been used for a nephrectomy in a neonate as young as 3 weeks of age (El-Ghoneimi, 2005).



→ PORT PLACEMENT FOR LEFT RETROPERITONEAL LAPAROSCOPIC PYELOPLASTY

Describe a Lap Retroperitoneal Pyeloplasty.

A three-trocar technique is currently employed (El-Ghoneimi et al, 2003) (see Fig. 115-21). First, a 3- or 5-mm trocar for the laparoscope is placed (at the tip of the 12th rib), the second 3-mm trocar is inserted in the costovertebral angle (used for the needle driver on the left side pyeloplasty), and the third trocar is inserted at the top of the iliac crest (used for the needle driver on the right side pyeloplasty). The kidney is approached posteriorly and the renal pelvis is first identified. The pyeloureteral junction is identified and minimal dissection is done to free the junction from connective tissue. Small vessels are divided using bipolar electrocoagulation. Care is taken not to section ureteral blood vessels. A stay suture is placed at the junction (Fig. 115-23). Aberrant crossing vessels are identified. The renal pelvis is partially divided using scissors at the most dependent part, and gentle traction on the stay suture helps to define this point. Keeping the traction, the ureter is partially divided and incised vertically for spatulation. The traction suture helps to mobilize the ureter so that the scissors can be in the axis of the ureter, usually introduced through the last trocar. The anterior surface of the kidney is left adherent to the peritoneum so that the kidney is retracted medially without the need for individual kidney retraction.

The ureteropelvic anastomosis begins using a 6-0 absorbable suture with a tapered 3/8 circle needle, placed from the most dependent portion of the pelvis to the most inferior point or vertex of the ureteral spatulation. The suture is tied using the intracorporeal technique with the knots placed outside the lumen. The same stitch is used to run the anterior wall of the anastomosis. The UPJ is kept intact for traction and stabilization of the suture line and removed just before tying the last suture on the pelvis. This stay suture may be fixed to the psoas muscle to give stability and to facilitate the suturing. A double-pigtail stent is inserted through the costovertebral angle trocar, and, if there is doubt, its position in the bladder is ensured under fluoroscopy. The posterior ureteropelvic anastomosis is then done. To avoid a second general anesthesia to remove the stent, a transanastomotic pyelostomy stent is used. The stent is closed on the first postoperative day and removed at 1 week in the outpatient clinic. A double-pigtail stent is used with an intrarenal pelvis because of the technical difficulties of inserting the pyelostomy stent. The pelvis is trimmed if needed. In case of aberrant crossing vessels (Fig. 115-24), the technique is slightly different. After placement of the stay suture, the ureter is completely divided and the UPJ and the pelvis are delivered anterior to the vessels with the help of the stay suture. Then the anastomosis is performed as described. If a double J stent is used, a Foley catheter is left in the bladder for 24 hours postoperatively.

Describe gaining transperitoneal access for a Lap Pyeloplasty.

Several options exist for positioning the patient. The most frequently described is the flank position (Peters, 2000). The pneumoperitoneum is created through an open umbilical approach. The child is positioned with the surgeon standing in front of the abdomen (opposite side of pyeloplasty) (Fig. 115-22A). The most frequent configuration has been an umbilical port and two ipsilateral ports in the midclavicular line above and below the umbilicus. A fourth trocar may be placed in the midaxillary line to allow liver or spleen retraction, if needed. The kidney is exposed by medial mobilization of the colon. Ideally, the laparoscope is placed through the umbilicus, and the operating trocars are inserted midway between the umbilicus and the symphysis pubis and between the umbilicus and the xiphoid process (Fig. 115-22B). This configuration is available for both sides and has been used successfully in cases of horseshoe kidney.



→ PORT PLACEMENT FOR TRANSPERITONEAL LAPAROSCOPIC PYELOPLASTY

What special situations may be encountered that may affect the approach for UPJO repair?

- hydronephrosis due to low UPJ
- retrocaval ureter
- horseshoe kidney
- ectopic kidney
- ureterocaliceal anastomosis
- redo surgery
- lateral retroperitoneal approach can deal w/ most of these situations EXCEPT for horseshoe kidney & ectopic kidneys
 - transperitoneal is better for these cases
- lateral retroperitoneal approach may be better for re-do if previously done transperitoneally
 - if done retroperitoneally previously then transperitoneal approach is likely better

List techniques used when there is inadequate ureteral length during pyeloplasty.

- pelvic flap
- renal descensus
- ureterocalicostomy
- ileal interposition
- auto-Tx

OUTCOME

What is the definition of a successful UPJO repair?

- improvement in hydronephrosis
- stabilization or improvement in renal function on renal scans with decrease in $T_{1/2}$
- resolution of symptoms

How successful is pyeloplasty for UPJO?

- >90% in most series

What are the potential complications of pyeloplasty for UPJO?

- early
 - prolonged urine leak
 - infection
 - bleeding
 - intraperitoneal organ injury } bowel, spleen, liver, etc
- late
 - recurrence of UPJO
 - urinoma
 - worsening of renal function
 - worsening of hydronephrosis

What are the options after a failed pyeloplasty?

- **better to wait at least 2 months before attempting repair**
- endopyelotomy } good success rate because ureter now sits in dependent position
- redo pyeloplasty } successful in most cases
- ureterocalicostomy } if evidence of extensive proximal ureteral strictures, intrarenal pelvis, or diminished pelvis that prevents tension-free anastomosis
- nephrectomy

Chapter #116 – Ectopic Ureter, Ureterocele, and other Ureteric Anomalies

TERMINOLOGY

What is a duplex kidney?

- kidney that has 2 separate pelvicalyceal systems } has an UP and a LP
- ureters may join at any point
 - if they join at level of UPJ, it's termed a BIFID SYSTEM
 - if they join distal to UPJ but proximal to bladder, it's termed BIFID URETERS
- if they don't join and drain their respective poles & empty separately into the GU tract, there is a complete duplication
 - it's termed DOUBLE URETERS

What is an ectopic ureter?

- any ureter whose orifice terminates anywhere other than the N trigonal position
 - lateral ectopia } a ureter that inserts more lateral and cranial than normal
 - caudal ectopia } a ureter that inserts more medial and distal than normal
- **in general practice, “ectopic ureter” refers to a ureter that inserts more caudal than the bladder neck, such as the urethra or outside the GU tract**

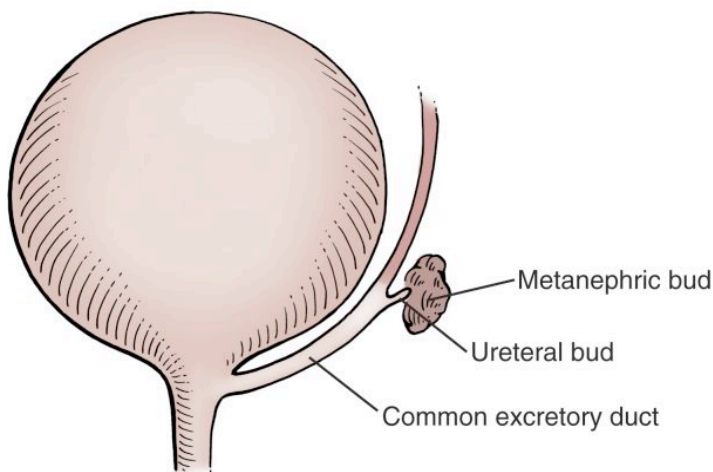
What is a ureterocele?

- cystic dilatation of the distal most part of the ureter
 - ???due to a persistence of Chwalla's membrane
- **Committee on Terminology, Nomenclature, & Classification of the Section of Urology '84**
 - a) LOCATION } intravesical vs ectopic**
 - intravesical is contained within bladder in its entirety
 - ectopic if any portion of ureterocele extends to BN or urethra
 - b) SYSTEM } single vs duplex**
 - according to # of systems
 - c) ORIFICE } stenotic vs sphincteric vs sphincterostenotic vs cecoureterocele**
 - stenotic is narrowed or pinpoint orifice
 - sphincteric is orifice distal to BN
 - sphincterostenotic is narrowed or pinpoint orifice & distal to BN
 - cecoureterocele is intravesical orifice but submucosal extension that dips into the urethra
 - intravesical ureteroceles can only be stenotic

EMBRYOLOGY

What is the embryologic beginnings of the upper collecting system?

- at **4 wks gestation, ureteric bud arises** from the distal mesonephric duct and interacts w/ the metanephric blastema
 - the interaction between the ureteric bud & metanephric blastema results in the branching and development of the ureteric bud into the calyces, renal pelvis, and ureter
 - N interaction is also necessary for development of metanephric blastema into a N kidney
 - segment of mesonephric duct distal to ureteric bud is the **common excretory duct**
 - **point of origin of ureteric bud off distal mesonephric duct is the ureteric orifice**
 - once UO enters bladder, it migrates in cranial & lateral direction
 - if ureteric bud comes off mesonephric duct more distally than normal, it enters bladder early and then migrates even further cranial and lateral than usual (**lateral ectopia**)
 - if ureteric bud comes off mesonephric duct more proximally than normal, it enters bladder late and has less time to undergo normal migration, resulting in UO that is more medial and caudal than usual (**caudal ectopia**)
 - if ureteric bud comes off mesonephric duct even more proximal, the UO may remain on the mesonephric duct, resulting in a UO outside the bladder altogether
 - if ureteric bud becomes bifid AFTER emerging from mesonephric duct, then this results in a duplex kidney with a bifid ureter
 - if 2 separate ureteric buds originate from the mesonephric duct, then a complete duplication occurs with double ureters
- *** THE MORE PROXIMAL THE URETERIC BUD COMES OFF THE MESONEPHRIC DUCT, THE MORE DISTAL AND MEDIAL THE UO ENDS UP ***
- *** ABNORMAL ORIFICE IS LIKELY ASSOCIATED WITH ABNORMAL KIDNEY ***



→ EMBRYOLOGIC BEGINNINGS OF THE GU TRACT

What are the embryologic equivalents of the mesonephric duct?

- **male } efferent ductules, epididymis, vas deferens, SVs, ejaculatory duct**
- **female } epoophoron, oophoron, and Gartner's duct**
- ectopic ureter can insert into any of these structures } **males never incontinent**
- in females, can rupture into adjoining fallopian tube, uterus, upper vagina, or vestibule and result in incontinence

What is the Weigert-Meyer rule for complete duplicated systems?

- UP } usually inserts distal & medial → associated with obstruction and ureterocele
- LP } usually inserts cranial & lateral → associated with reflux and UPJO

ANOMALIES OF TERMINATION (ECTOPIC URETERS)

What is the epidemiology of ectopic ureters?

- “ectopic” meaning inserting at BN or distally into mesonephric duct structure
- true incidence unknown because many are asymptomatic
- more common in F (2-3x)
- **80% are associated with a duplicated collecting system**
 - in females, >80% duplicated
 - in males, most drain single systems } especially if ectopic ureterocele are excluded
- 5-15% appear bilaterally
- often see unilateral ectopic ureter + contralateral duplicated system
- ectopic ureter itself is often abN } more so in single system
- **most ectopic ureters drain renal moieties (UP or single-system kidney) that have minimal function**
- renal units drained by ectopic ureters have problems with proper development

Where are the most common sites of termination of an ectopic ureter (CHART)?

→ **the more remote the ureteral opening, the greater the degree of renal maldevelopment**
eg. hypoplasia/dysplasia of an UP segment in a duplicated system

→ males

- **posterior urethra/BN (~50%)**
- SV (33%)
- prostatic utricle (10%)
- ejaculatory duct (5%)
- vas deferens (5%)

→ females

- **urethra (35%)**
- vestibule (34%)
- vagina (25%)
- cervix/uterus (5%)
- urethral tic (<1%)
- Gartner’s duct (<1%)

What other anomalies are associated with ectopic ureters?

- renal abnormalities
- imperforate anus
- TE fistula
- duplicated vagina or hemivagina
- bicornuate uterus

How does an ectopic ureter usually present?

→ males

- **never incontinent } never distal to EUS**
- **UTIs**
- **epididymitis } insertion into Wolffian duct structures**
- urgency and frequency
- constipation
- painful ejaculation

→ females

- **total urinary incontinence w/ otherwise N voiding pattern after toilet training**
- persistent vaginal discharge
- **acute or recurrent UTIs**
- FTT
- chronic infection
- urge incontinence

→ abdominal mass } massive hydronephrosis & hydroureter

→ abdominal/pelvic pain (obstruction)

How is the Dx of an ectopic ureter made?

- antenatal U/S
 - classically see hydronephrosis in UP of duplex kidney + N bladder
- P/E in female may reveal direct visualization of continuous urinary dribbling/wetness
 - need to r/o neurogenic bladder dysfunction and/or urethral sphincter defect
 - look for erythema from irritated genital/perineal skin
- U/S findings
 - dilated UP collecting system + N bladder
 - “pseudoureterocele” from large ectopic ureter pressing against bladder
 - “ureterocele” is extravescical & usually has thick septum b/w bladder and lumen
- IVP can confirm Dx (see below)
- VCUG
 - may have VUR into LP ureter (50%)
 - may also see VUR into ectopic ureter at different phases of voiding, showing evidence of the location of the orifice
 - if VUR seen before voiding, ectopic ureter likely proximal to BN
 - if VUR only seen with voiding, ectopic ureter drains into urethra
- contrast CT or MRI
 - may be required to visualize small UP segment associated with ectopic ureter that isn’t seen on IVP or U/S
- cystourethroscopy and vaginoscopy
 - ectopic ureteral orifice may be identified } perform retrograde pyelogram to confirm
 - look for absent ipsilateral hemitrigone

What are the IVP findings suggestive of an ectopic ureter in a duplex system?

- 1) non or poorly visualized UP of a duplex system that may be massively hydronephrotic
 - 2) UP displaces LP downward & outward } **“drooping lily”**
 - 3) if UP is non-visualized
 - a) the LP has fewer calyces than normal kidney
 - b) axis of lower to uppermost calyx doesn’t point toward midline
 - c) uppermost calyx of LP is usually farther from UP border than is the lowest calyx from the corresponding LP limit
 - d) LP pelvis and upper portion of its ureter is farther from spine than on contralateral side
 - e) LP ureter may be scalloped & tortuous from its wrapping around a markedly dilated UP ureter
- ➔ **if ectopic ureter is associated with dysplastic single kidney then these typical features may not be seen**

What are the advantages of MRI in diagnosing an ectopic ureter with a small dysplastic UP moiety?

- no contrast needed
- no radiation
- T2-weighted images excellent at finding fluid-filled structures such as the ectopic ureter
- sagittal view excellent at showing exact insertion point of an ectopic ureter
- may add info re: other abN’s of the internal reproductive system

What are the surgical options for an ectopic ureter?

→ **most ectopic ureters drain renal moieties that have minimal function**

→ non-salvageable renal moiety

1) UP nephrectomy (total nephrectomy for single system)

- open, lap, or robot-assisted lap approaches
- for heminephrectomy, must be careful not to damage viable LP vessels
 - transection of UP ureter and placement of traction stitch on proximal portion of this ureter gives good retraction and manipulation of UP moiety
- must also be mindful not to compromise vascular supply of LP ureter
- if concomitant VUR into ectopic ureter, then 2nd Gibson incision needed to resect ureter in its entirety
 - hard to separate distal 2-3cm of UP ureter from LP ureter so leave back wall of the UP ureter to preserve blood supply to LP ureter
 - be mindful of vas deferens also

2) renal embolization

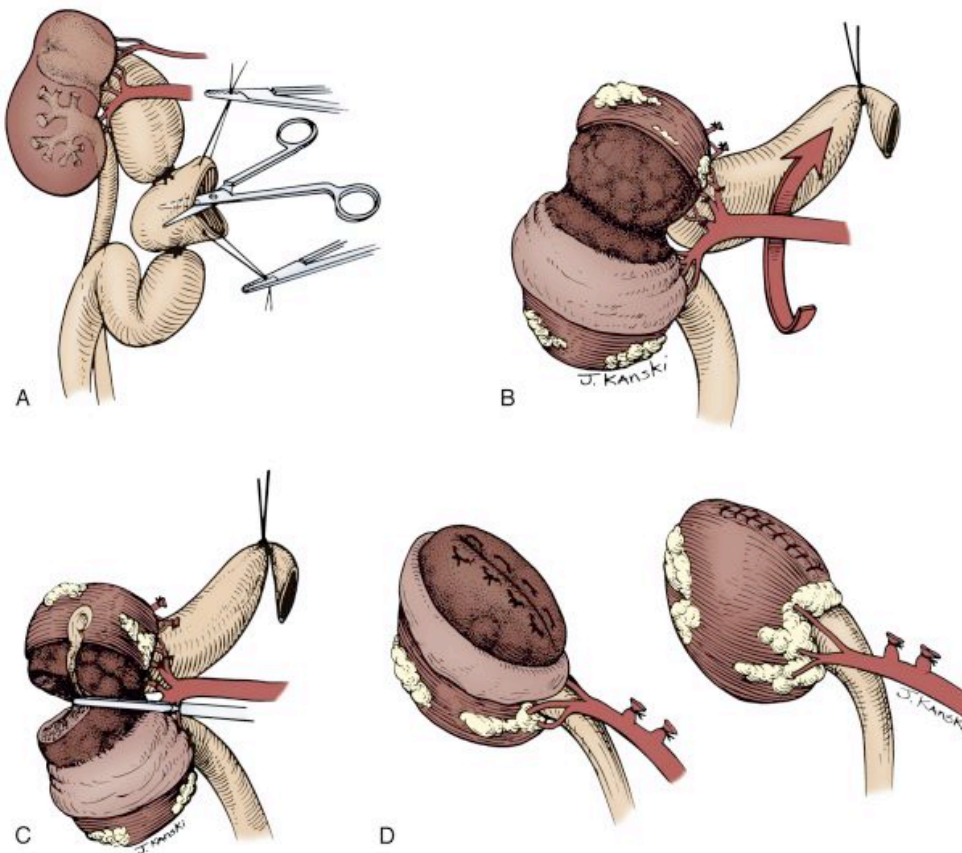
- if single-system kidney with scant function

→ if renal function worth salvaging

- 1) ureteropyelostomy or common sheath ureteral reimplantation for duplicated system
- 2) solitary reimplantation for a single system
- 3) endoscopic dilation of insertion site if ectopic ureter inserts proximal to sphincter

→ JP drain to drain renal fossa and area of ureteral dissection

→ IVP or renal scan to confirm LP function



→ UPPER POLE Nx FOR ECTOPIC URETER ASSOCIATED WITH MINIMALLY FUNCTIONING UPPER POLE MOIETY

What is the significance of bilateral single-system ectopic ureters?

- uncommon } occurs in only 5-15%
 } usually drains into distal urethra in females & prostatic urethra in males
 - kidneys are often dysplastic or display varying degrees of hydronephrosis
 - VUR often present
 - BN often incompetent } continued leakage leads to small capacity bladder (less so in males)
- Rx → ureteral reimplantation + reconstruction of BN for continence (Young-Dees-Leadbetter, Pippi-Salle, or Kropp)
- success rate higher in boys
 - bladder capacity often increases if incontinence if fixed } may need bladder augment to increase bladder capacity

ANOMALIES OF STRUCTURE (URETEROCELES)

What is the epidemiology of ureterocele?

- cystic dilatation of the terminal ureter
- **4x more common in F**
- almost exclusively in whites
- **10% are bilateral**
- **80% arise from UP of a duplicated system**
 - single-system ureterocele usually orthotopic } less prone to severe obstruction & dysplasia
 - single-system ureterocele more common in boys and in adults
- **ipsilateral LP VUR (60%) and contralateral VUR (10%)**
- can be ectopically located
 - **bilateral ectopic ureterocele assoc'd w/ poor bladder emptying & recurrent UTIs even after surgical treatment**
- recommended imaging for Work-up } U/S, VCUG, renal scan

What are the proposed theories explaining the etiology of a ureterocele?

- 1) incomplete dissolution of Chwalla's membrane
- 2) abN muscular development
- 3) developmental stimulus responsible for bladder expansion that also affects intravesical ureter

How do ureterocele present?

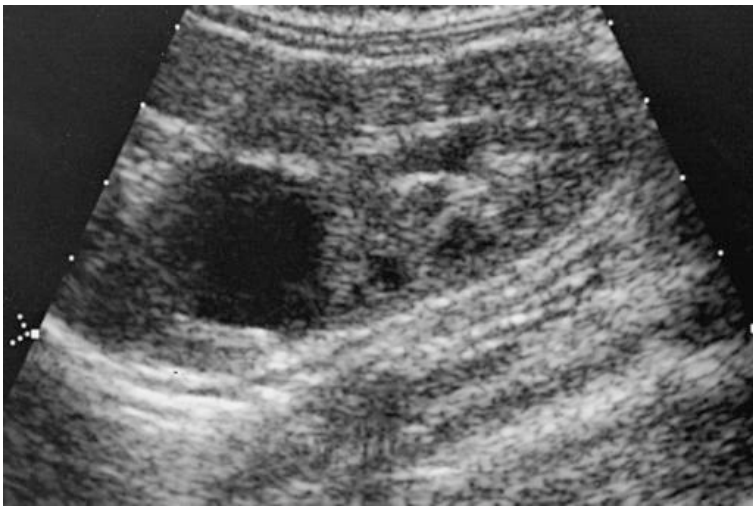
- many are detected antenatally
 - hydronephrosis + intravesical cystic dilatation
 - MRI can be useful for equivocal U/S
- many still diagnosed clinically
 - UTI or sepsis +/- stone
 - palpable abdominal mass (hydronephrotic kidney)
 - vaginal mass (ectopic and prolapsing out urethra)
 - BOO (if large enough)
 - incontinence (ectopic ureterocele interferes with normal sphincter function)
 - hematuria
- may have insidious clinical course
 - FTT
 - vague abdo/pelvic pain

What is the classification of ureterocele?

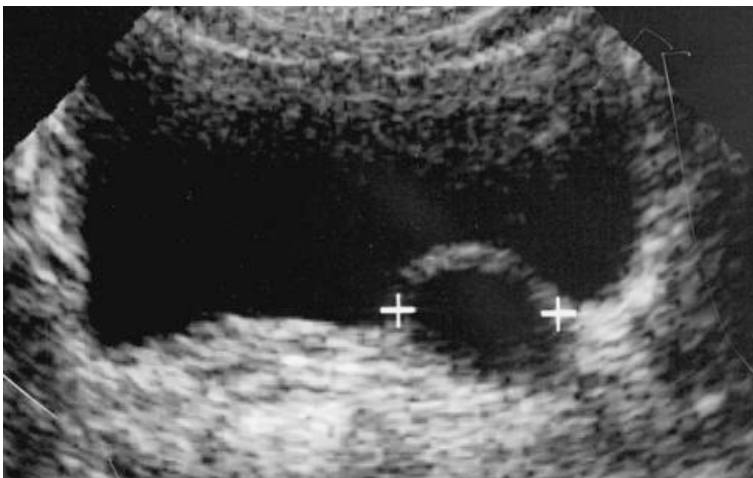
- location } orthotopic vs ectopic
- collecting system } single vs duplex
- orifice } stenotic vs sphincteric vs sphincterostenotic vs cecoureterocele

What are the U/S findings suggestive of a ureterocele?

- usually associated with duplicated system
 - 1) hydronephrotic UP moiety with dilated ureter
 - 2) LP may also have hydronephrosis if associated with VUR or if ureterocele causes delayed emptying from ipsilateral LP
 - 3) bilateral hydronephrosis } if large enough to obstruct contralateral UO or BN
 - 4) UP moiety parenchyma shows varying degrees of thickness and echogenicity
 - 5) thin-walled intravesical cyst
- ensure bladder not too full (effaced ureterocele may go unnoticed) and not empty (hard to discriminate wall of ureterocele from wall of bladder)
- may see “ureterocele disproportion” (UP moiety so small & dysplastic that it’s not seen and ureter is not dilated)
- dilated ectopic ureter pressing on bladder wall may look like “pseudoureterocele”



→ U/S IMAGE OF UPPER POLE HYDRONEPHROSIS FROM A URETEROCELE

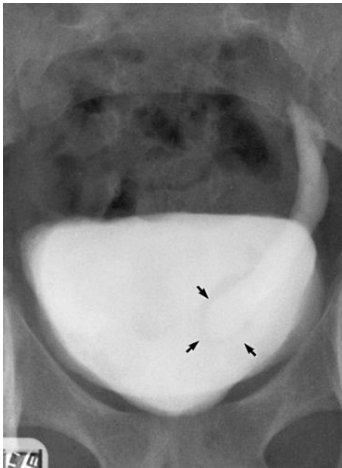


→ U/S IMAGE OF INTRAVESICAL URETEROCELE

What are the IVP findings suggestive of a ureterocele?

→ usually associated with duplicated system

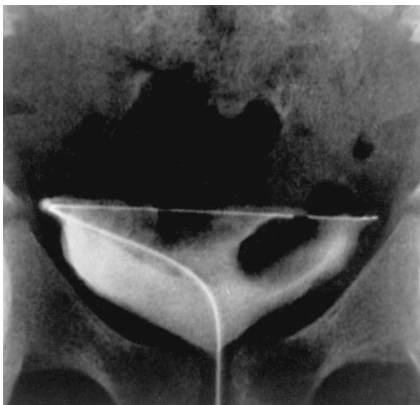
- 1) laterally deviated UP (from hydronephrosis) with delayed or no excretion of contrast
 - 2) LP deviated laterally and inferiorly (UP hydro) } “**drooping lily**” sign
 - 3) laterally deviated, serpiginous, notched LP ureter } from dilated tortuous UP ureter
 - 4) decreased # of calyces } only LP may be seen
 - 5) hydronephrosis of contralateral kidney } from obstructing ureterocele
- may see “**cobra-head**” if orthotopic ureterocele with functional renal unit due to filling defect of ureterocele wall



→ IVP IMAGE OF LEFT URETEROCELE } “Cobra head”

What are the VCUG findings suggestive of a ureterocele?

- large, smooth cystic filling defect in near trigone } seen best earlier in filling phase (if too full, ureterocele may be effaced)
- VUR into ipsilateral LP moiety common (~50%)
- may see VUR into contralateral kidney if ureterocele large enough to distort trigone (~10%)



→ CYSTOGRAM OUTLINING LARGE LEFT URETEROCELE

What is the role of renal nuclear scans in assessing ureteroceles?

- used to assess contribution of UP to overall renal function } salvageability
- also can assess degrees of obstruction

What are the goals of treating ureterocele?

- 1) preservation of renal function
 - preservation of UP renal fxn seen only in ~1/3 } usually contributes little, if at all, to overall renal function to begin with
 - **preservation rate similar for intravesical vs ectopic ureterocele and also for antenatal vs postnatal Dx**
- 2) elimination of infection
- 3) elimination of obstruction and reflux (one may lead to the other)
- 4) maintenance of urinary continence
- 5) minimize surgical morbidity

What are the management options for ureterocele?

→ **early institution of daily prophylactic ABx** } decreases rate of UTIs

→ must consider each case individually

→ **SINGLE-SYSTEM** (less common)

- 1) endoscopic decompression +/- correction of VUR (if salvageable kidney)
 - **less likely to see reflux in single-system (orthotopic) cf ectopic ureterocele**
- 2) transvesical excision of ureterocele + reimplantation (if salvageable kidney)
- 3) Nx (non-salvageable kidney)
 - uncommon b/c usually NOT severely obstructing

→ **DUPLEX SYSTEM** (more common)

→ **depends on function of UP moiety**

1) **upper tract approach**

- a) UP nephrectomy + partial/total ureterectomy (non-fxn'l UP moiety)
- b) ipsilateral ureteropyelostomy or proximal UU (if salvageable UP function)
 - results in decompression of ureterocele + possible resolution of ipsilateral LP reflux
 - 2nd OR if persistent LP VUR, VUR into ureteral stump, or failure of ureterocele decompression
 - need 2nd OR in 20-40% } more if LP VUR is high-grade

2) **combined upper & lower tract approach**

- a) UP nephroureterectomy + excision of ureterocele + LP ureteral reimplantation (non-fxn'l UP)
- b) UP nephrectomy + partial ureterectomy + intravesical excision & marsupialization of ureterocele + correction of reflux (non-fxn'l UP)
 - 2nd OR in only ~15% (usually for reflux)

3) **lower tract approach**

- a) ureterocele excision + common sheath reimplantation of UP & LP ureters (if salvageable UP)
- b) endoscopic approach (if salvageable UP function)
 - puncture or incision of ureterocele
 - **only 30-40% need 2nd OR } outpatient OR with minimal morbidity**
 - } 1st line in most cases**
 - not 1st line if ectopic ureterocele } high rate of 2nd OR (VUR in ~80%)

What are the benefits of the upper tract approach & the combined upper and lower tract approach?

Upper tract approach	combined approach
- can avoid 2 nd OR in 60-80%	- more likely to avoid 2 nd OR
- avoid complex dissection near BN	- better outcomes if presence of VUR or ectopic ureterocele
- single incision site	
→ not good if VUR into ipsilateral LP	

What is the management of choice if a patient with a ureterocele is septic and not responding to ABx?

→ **decompression via endoscopic incision**

What is the impact of timing of Dx on success rates of ureterocele procedures?

- preservation of renal function } similar between antenatal & postnatal Dx
- need for 2nd OR } more common with postnatal Dx (45% vs only 22% if antenatally Dx'd)
 - } worse for both if endoscopic decompression approach used

What are the principles of endoscopic decompression of ureterocele?

- don't pass cystoscope blindly as it may tear ureterocele
- incise/puncture as distally as possible and as close to bladder floor as possible
→ makes flap that decreases risk of post-op reflux
- incise full thickness of ureterocele wall
→ often thick walled
- if ectopic ureterocele extending into urethra, consider longitudinal incision from intravesical portion down into urethral portion
→ can also make 2 separate punctures, one in intravesical portion & another in urethral portion of ureterocele

What is the management of a ureterocele associated with a MCDK moiety?

- usually have no reflux or only low-grade reflux } don't see ureteral dilatation
- most followed expectantly with success

What is the management of a prolapsing ureterocele?

- DDx of interlabial mass
- stable patient
 - manually reduce prolapsing ureterocele back into bladder } often recurs
 - UP nephrectomy + aspiration of ureterocele
- acutely sick child
 - transverse incision into ureterocele at level of vagina } not always definitive
 - endoscopic incision of ureterocele in its intravesical portion
 - open surgical unroofing or marsupialization } common sheath reimplant at later date

What is the DDx of an interlabial mass in a young girl?

- prolapsed ureterocele
- prolapsed urethra (uncommon in newborn)
- urethral polyp/skin tag
- vaginal RMS (botryoid type)
- imperforate hymen (hydrometrocolpos)
- paraurethral cyst (skene's duct cyst – most common in neonate)

What other STRUCTURAL ureteral abnormalities have been described?

- 1) congenital ureteral stenosis & stricture } UPJ most common site, then distal ureter just above UVJ, and only rarely at pelvic brim
- 2) ureteral valves } transverse folds of redundant mucosa containing smooth muscle
 - } more common at UPJ and upper ureter
 - } no gender or side preference
 - } diaphragmatic annular valves are rare but a definite form of obstruction
 - } transverse non-obstructing mucosal folds found in 5% of ureters in newborns and gradually disappear with growth (Ostling's folds)
- 3) spiral twists and folds of the ureter
- 4) ureteral diverticula

What is the Gray & Skandalakis classification of ureteral diverticula?

- 1) abortive ureteral duplications (blind-ending bifid ureters)
→ from premature cleavage of ureteric bud with abortive development of accessory limb
- 2) true congenital diverticula containing all tissue layers of the normal ureter
→ abnormal ureteric bud development
- 3) acquired diverticula representing mucosal herniations
→ may be associated with strictures, stones, or trauma

ANOMALIES OF NUMBER (URETERAL DUPLICATIONS)

What is the epidemiology of ureteral duplication anomalies?

- incidence is ~0.8% (1 in 125)
 - autopsy data more accurate than determining incidence based on clinical series
- **slightly more common in F (1.6x)**
- UNILATERAL duplication 6x more common than bilateral duplication
- R = L
- incidence of bifid ureters = double ureters
- ureteral duplication may be an AD trait with incomplete penetrance
 - duplication more common in parents & siblings (~1 in 8)
- more common in patients with childhood UTIs } ??? selection bias

What is the location of the orifices with double ureters?

- **Weigert-Meyer rule holds** (there are rare exceptions that have been observed)
- UP orifice is more caudal and medial
- LP orifice is more cranial and lateral

What are some of the anatomic findings associated with ureteral duplication?

- 1/3 of renal parenchyma is drained by upper collecting system
- more calyces associated with duplex systems
 - usually 2x more calyces in LP than in UP moiety
- renal scarring, dilatation, and VUR more common in duplex kidney
- **LP segment associated with reflux and UP segment associated with obstruction**
- ureteroceles more common in UP segment

What other anomalies are associated with ureteral duplication anomalies?

- GU } renal dysplasia
- } ectopic UP ureter
- } VUR
- } UPJO
- GI tract abN's
- cardiopulmonary abN's

How common are blind-ending duplication anomalies of the ureter?

- likely a result of an abortive ureteric bud that failed to make contact with the metanephros
- rare (<70 cases)
- 3x more common in F } **2x more common on R side**
- blind end tends to have a bulbous dilation
- usually involves one limb of a bifid system rather than involving complete duplication
 - **Y junction of bifid type is usually found in mid to distal ureter**
- usually asymptomatic & don't present until 20s or 30s } vague abdo pain, chronic flank pain, infections, stones
- Rx → if symptomatic, excise blind segment, starting at most proximal end
 - don't enter normal ureter & compromise the common blood supply

How common are inverted-Y ureteral duplication anomalies?

- likely from 2 separate ureteric buds that fused into a single duct before joining metanephros
- rarest ureteral branching anomaly
- more common in F
- **one of the distal limbs often ends in an ectopic ureter or ureterocele**
- Rx → if symptomatic, resection of accessory channel usually directed at ectopic limb

What is the Smith classification of ureteral triplication?

- ureteral triplication associated with renal fusion anomalies, VUR, obstruction, ureteroceles, or ureteral ectopia
- 1) complete triplication } 3 ureters from kidney with 3 draining orifices (bladder, urethra, etc)
- 2) incomplete triplication } bifid ureter + single ureter, with 3 ureters from the kidney and 2 orifices draining below
- 3) **trifid ureter } all 3 ureters unite to drain through a single orifice**
→ **most common form**
- 4) 2 ureters from kidney with one becoming an inverse-Y bifurcation, resulting in 3 orifices

ANOMALIES OF POSITION

What vascular anomalies have been associated with ureteral obstruction?

→ **vascular system, NOT urinary system, is anomalous**

- 1) accessory renal blood vessel
 - accessory or aberrant vessels to LP of kidney can cross anterior to UPJ
- 2) retrocaval/circumcaval ureter
 - more accurate to call it “preureteral vena cava”
- 3) retroiliac ureter
 - “preureteral iliac artery”
- 4) vascular obstruction of distal ureter
 - uterine, umbilical, obturator, and internal iliac vessels
 - not clear if vascular impression is cause of obstruction
- 5) ureteric herniation
 - most are paraperitoneal
 - loop of herniated ureter extends alongside a peritoneal hernia sac
 - ureteral loop is ALWAYS MEDIAL to peritoneal sac
 - inguinal, scrotal, femoral herniations
 - acquired or congenital

What is a “retrocaval ureter”?

- abnormality of vascular system
- uncommon (1 in 1500 cadavers)
- 3-4x more common in M
- most don't present until in 20's to 30's
- involves R ureter } deviates medially behind IVC and then crosses in front of it, from medial to lateral, to resume a normal course distally
- **due to failure of subcardinal vein to atrophy**
 - persistent L subcardinal vein becomes primary R-sided vein, trapping ureter dorsal to it
- usually get elongated & dilated renal pelvis and upper ureter
 - J-hook/fishhook shape before passing behind IVC
 - obstruction not always found

What are the classifications of retrocaval ureters?

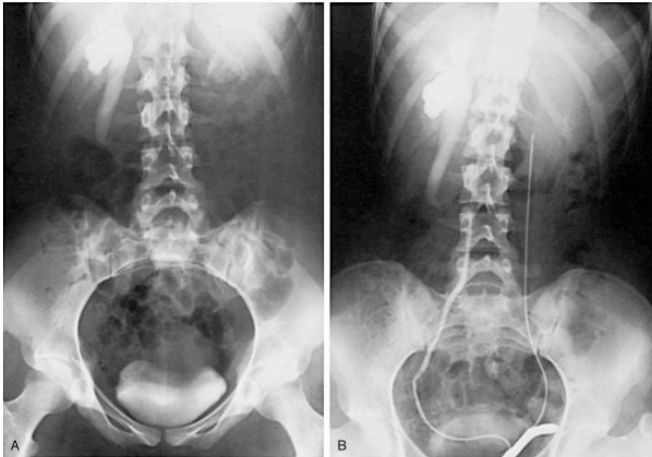
- classified into 2 different types
- type 1 } hydro + J-hook deformity (S-shaped)
 - } more common
 - } obstruction is at edge of iliopsoas muscle
- type 2 } little or no hydro (sickle-shaped)
 - } if present, obstruction occurs at lateral wall of IVC

Describe the embryologic formation of a preureteral vena cava.

- IVC develops on R side from fetal plexus of veins
 - posterior cardinal and supracardinal veins lie dorsally
 - subcardinal veins lie ventrally
- normally, L supracardinal veins and lumbar portion of R posterior cardinal vein atrophy
 - subcardinal veins become gonadal veins
 - **normal IVC forms from R supracardinal vein**
- **if R subcardinal vein fails to atrophy** and becomes the predominant R-sided vein, the ureter is trapped dorsally
 - if subcardinal & supracardinal vein both persist, double R IVC forms, trapping ureter b/w them

How does a retrocaval ureter present?

- incidentally
- flank pain
- abdo pain
- infection
- IVP, retrograde pyelogram, CT urogram, and MRI can all make Dx
- renal scan to assess for obstruction
- cavography not necessary



→ IVP AND RETROGRADE OF RIGHT RETROCAVAL URETER

What is the management of retrocaval ureter?

- ureteral division + relocation + UU or ureteropelvic reanastomosis
 - excision or bypass of retrocaval segment of ureter (often aperistaltic)
 - be mindful of ureter's blood supply from renal artery/aorta superiorly & iliac vessels inferiorly
- if solitary kidney, can consider division of anomalous IVC + repositioning behind ureter

What is a retroiliac ureter?

- vascular abnormality
- ureter courses behind iliac artery
- can involve either side } only few cases of bilateral disease
- **due to persistence of ventral root of umbilical artery as the dorsal root fails to form**
 - ventral root usually involutes by 4th wk of gestation
 - traps ureter dorsally
- obstruction occurs at L5 or S1 as ureter is compressed behind artery
- associated anomalies are common
 - ectopic ureter
 - mesonephric duct ectopia

Chapter #117 – Reflux and Megaureter

EMBRYOLOGY OF THE UVJ

What are the 2 main processes that govern the position & integrity of the UVJ?

- 1) interaction of ureteric bud (comes off distal mesonephric duct) with metanephric blastema at 4 weeks gestation
→ determines N development of upper collecting system and of kidney
- 2) timing of when ureteric bud comes off distal mesonephric duct
→ if bud comes off early (too distal), then enters UG sinus (becomes bladder) early and results in lateral ectopia + insufficient intramural length of ureter + reflux
→ if bud comes off late (too proximal), then enters UG sinus late & results in ectopia + obstruction
→ common excretory duct fuses into UG sinus to form trigone

FUNCTIONAL ANATOMY OF THE ANTI-REFLUX MECHANISM

What are the main factors that determine the presence of VUR?

- 1) functional integrity of the ureter
- 2) anatomic composition of the UVJ
- 3) functional compliance of the bladder

What are the key features of the intramural portion of the ureter that allow for an anti-refluxing valve?

- 1) adequate intramural length
→ **Paquin's 5:1 ratio** of tunnel length-to-ureter diameter
- 2) **fixation of ureter** between its extravesical & intravesical points

What happens to the 3 muscle layers of the ureter when the ureter reaches the bladder?

- 1) outer circular smooth muscle layer
→ merges w/ outer detrusor muscle to form Waldeyer's sheath
- 2) inner longitudinal smooth muscle layer
→ merges w/ detrusor muscle intravesically to contribute to superficial trigone
→ some fibers also contribute to intertrigonal ridge (Mercier's bar)
- 3) 3rd outermost layer exists in distal ureter

ETIOLOGY OF VUR

What are the causes of VUR?

- not always mutually exclusive
- **primary** } fundamental deficiency in UVJ anti-reflux mechanism with N bladder & ureter
 - lack of 5:1 ratio of ureteral length:width
 - usually d.t. a short intramural ureter
 - may also be d.t. excessive ureteral diameter
- **secondary** } normal UVJ function that is overwhelmed
 - usually due to bladder dysfunction (congenital, acquired, or behavioural)
 - also if there was a period of documented absence of VUR

What is the most common UDS finding in a kid with VUR?

- **uninhibited bladder contractions** } seen in 75% of girls with VUR

List some of the causes of secondary VUR?

- mechanical obstruction
 - PUVs } reflux found in 50-70%
 - } resolution of reflux seen in 1/3 of patients after relief of BOO
 - prolapsing ureterocele in girls } VUR in contralateral ureter resolves with mgt of ureterocele
- functional obstruction
 - neurogenic bladder
 - high bladder pressures seen during voiding in young infants } usually d.t. inadequate sphincter relaxation
 - } VUR resolves w/ normalization of UDS parameters as infant grows
 - dysfunctional voiding in older kids } creates high bladder pressures
 - } learned during toilet-training, d.t. constipation, etc
 - uninhibited bladder contractions } can cause secondary VUR but can also perpetuate 1° VUR
- ureteric abN'ity
 - UTI } atony from bacterial endotoxins

UTIs AND REFLUX

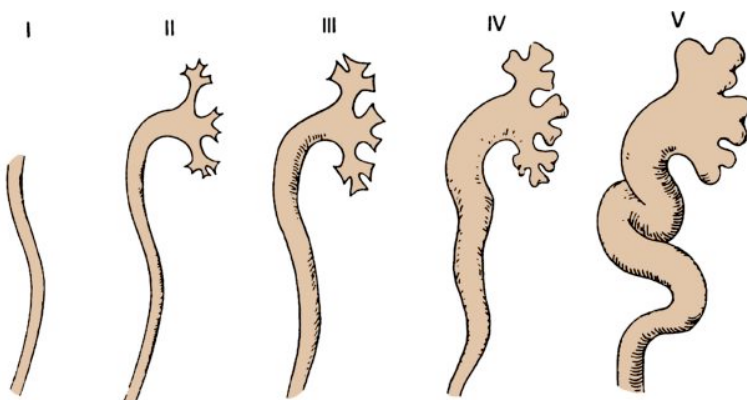
What is the relationship between VUR and UTIs?

- VUR does not generally cause UTI
 - infection may perpetuate VUR
 - VUR facilitates pyelonephritis
- VUR found in ~30-50% of kids with UTI } varies with age (up to 70% if <1yr of age)

GRADING OF REFLUX

What is the International Reflux Study Committee (IRSC) grading system of VUR?

- main role is to help prognosticate spontaneous resolution & for comparative research purposes
- Grade 1 } into a non-dilated ureter
- Grade 2 } into pelvis & calyces but without dilatation
- Grade 3 } mild to moderate dilatation of ureter, renal pelvis, and calyces
 } minimal blunting of fornices
- Grade 4 } moderate ureteral tortuosity with moderate dilatation of the renal pelvis and calyces
- Grade 5 } severe tortuosity of ureter with severe dilatation of renal pelvis and calyces
 } loss of papillary impressions (blunting of ALL calyces)



→ IRSC GRADES OF REFLUX

What are some limitations of the IRSC grading system of VUR?

- expected concordance between ureteral & calyceal dilation does not always occur
- in these discordant systems, it's unknown whether scarring after infection still occurs in same way
- in these discordant systems, it's unknown whether reflux resolves with age

What is the role of radionuclide cystography (RNC) to grade reflux?

- can be used instead of VCUG } much more sensitive in detecting presence of VUR
 } may miss very low grade VUR (scatter from bladder)
 - can't provide anatomic detail of bladder nor provide discrete images of ureter & calyceal structure
- 3 point grading system } low (IRSC 1), intermediate (IRSC 2-3), and high grade (IRSC 4-5)

DIAGNOSIS AND EVALUATION OF VUR

What is the best way to obtain a urine sample for C&S?

- confirming –ve culture is just as important as documenting non-contaminated UTI
- applies to patients with and without VUR
- **S/P aspiration is the most accurate, but also the most invasive**
- in kids that can void spontaneously, a clean voided MSU specimen is preferred
- catheterized specimen is more accurate than collection bag specimen
 - catheterized specimen not totally reliable, especially if uncx'd boy with phimosis
 - **collection bag specimen most useful if C&S is negative**
- must correlate R&M with C&S result
 - although, even colonization (+ve C&S w/ no pyuria on R&M) may be significant in VUR

What are the indications for imaging studies/VCUG in a kid with a UTI?

- 30-50% of kids with UTI are found to have VUR } higher if younger
- 1) all kids with febrile UTI
 - 2) any M with a UTI (unless he's sexually active)
 - 3) UTI in kids <5yrs of age (may not be done clinically in all cases – eg toilet trained 4yo F)

What imaging modality is used to assess for VUR?

- **U/S is 1st line imaging modality**
- add VCUG if any presence of structural renal anomalies, significant asymmetry, or if child is high risk for renal scarring (eg younger age, febrile UTI)
 - **VCUG is the gold standard study to detect VUR (cyclic study better)**
 - nuclear cystogram is more sensitive than VCUG but provides less anatomic detail
 - colour Doppler U/S has also been used in order to decrease radiation exposure
 - more sensitive with use of echo-enhancing contrast agents
 - limited use in infants/neonates
- **routine cystoscopy is contraindicated in VUR management**
- upper tract assessment is based on serial studies
- issue is differentiating congenital VUR-assoc'd renal dysmorphism from scarring acq'd from infections

List differences between antenatal VUR & VUR found in school age children.

	ANTENATAL	SCHOOL AGE
Etiology	- primary VUR more common	- more likely secondary (dysfxn'l voiders)
Resolution Rate	- resolution more common	- resolution uncommon
Severity	- higher grade VUR	- lower grade VUR
	- more likely bilateral	- more likely unilateral
Sex predilection	- more common in M	- more common in F
Need for ABx	- ABx prophylaxis required	- Abx not necessarily required

ASSESSMENT OF THE LOWER URINARY TRACT

What are the 3 different approaches used to perform cystography?

- indirect cystography } after excretory urography
- direct cystography } retrograde instillation
 - a) VCUG
 - b) RNC
- sonographic detection (color Doppler)

What factors can result in inaccurate assessment of VUR on VCUG or RNC?

- false -ve
 - not enough contrast instilled
 - pt unable to void and VUR only present during active bladder contraction
 - VUR that is only present during UTI
 - single filling-voiding cycle } 10-20% more VUR detected with cyclic VCUG
 - excessive hydration } diuresis may blunt retrograde flow
- false +ve
 - overfilling of bladder
 - ? infection

What is the significance of VUR seen on filling of bladder?

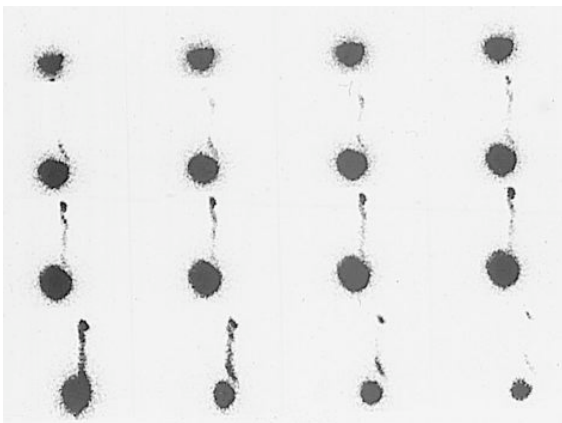
- worse prognosis } less likely to see spontaneous resolution of VUR

What are the main steps of a VCUG?

- scout film
- insertion of catheter
- film in early filling phase } some ureteroceles become effaced once bladder full
- filling under gravity
- film at bladder capacity } bladder capacity, bladder and BN contour, presence of tics or ureteroceles, grade of VUR, etc
- voiding phase film
- post-void film } delayed clearance of contrast from upper tract, significance PVR

What are the advantages & disadvantages of RNC compared to VCUG?

- | | |
|--|--|
| → advantages | → disadvantages |
| <ul style="list-style-type: none">- less radiation- greater sensitivity for grade 2-5 | <ul style="list-style-type: none">- poor sensitivity for grade 1 VUR- more expensive- less anatomic detail |



→ RADIONUCLIDE CYSTOGRAM } RIGHT-SIDED VUR (worsens with filling)

What is the role of uroflowmetry & urodynamics in assessing VUR?

- 1) uroflowmetry
 - **r/o low flow rate related to incomplete relaxation of the bladder outlet**
 - high pressure voiding may delay natural resolution of VUR or even perpetuate it
 - increased **PVR** may be a risk factor for UTI
- 2) UDS
 - full UDS not required in all VUR patients

What is the role of cystoscopy and PIC cystograms in assessing VUR?

- 1) **ROUTINE CYSTOSCOPY CONTRAINDICATED IN MGT OF VUR**
- 2) PIC Cystogram (positioning instillation of contrast)
 - controversial
 - purports to detect VUR under GA in patients with febrile UTIs but a normal VCUG
 - contrast instilled under low pressure directly toward UO under cystoscopic vision and simultaneous fluoroscopy
 - DOESN'T allow for age-adjusted instillation pressures
 - mgt of recurrent febrile UTIs, despite normal VCUGs, is prophylactic Abx anyway
 - benefit is that endoscopic correction could take place right after PIC cystogram

ASSESSMENT OF THE UPPER URINARY TRACT

What is the role of serial upper tract imaging in the management of VUR?

- assessing for evidence of impediments on renal growth related to renal scarring due to pyelonephritis
- allows MD to ascertain whether abN'ities are due to ongoing or resolved VUR and to differentiate them from intrinsic developmental disturbances, medical renal disease, or obstruction
- **meta-analysis showed no value in routine imaging of upper tracts for VUR with respect to preventing renal damage**

What are the different modalities used to assess the affects of VUR on the kidneys?

- 1) U/S } serial f/u of renal growth and development
 - } can also assess degree of corticomedullary differentiation in the kidney
 - loss of CM differentiation (or increased echogenicity) is associated with some degree of renal functional impairment
 - may represent congenital dysplasia
 - } can't absolutely r/o or confirm VUR on U/S
 - variable dilatation may suggest reflux
 - increased renal RI's may suggest reflux
- 2) renal scans } **gold standard to assess functional renal parenchyma**
 - } can be used to assess progression of scarring (which may prompt Rx of VUR) and can influence management decisions (based on differential function)
 - } **DMSA is ideal**
 - "tubular tracer" } 65% secretion + 35% filtration
 - good estimation of renal scarring and pyelonephritis
 - NOT ALL DMSA defects are scars or due to infection
 - could be congenital cortical defect
 - not used if <3mos of age } immature tubules don't take up tracer well
 - } MAG3 preferred
- 3) SPECT } higher sensitivity for detecting scars compared to standard renal scans
 - } doesn't add much to standard renal scans wrt the clinical mgt of VUR



CORTICAL DEFECTS

What factors affect likelihood of urinary tract infections in kids?

- 1) bacterial virulence factors } adherence (P pili, etc)
- 2) host factors } susceptibility to infection (immune response, urine dwell time, etc)
- 3) local factors } hygiene, circumcision, bowel habits, etc

What are the long-term sequelae of VUR?

- 1) HTN (33%)
 - more common with more severe VUR
 - exact etiology is unknown } may be more related to congenital renal dysplasia assoc'd w/ VUR not acquired scarring from infections
- 2) renal growth impairment (mainly related to # and type of UTIs)
 - correction of VUR does not predict catch-up growth
 - contralateral compensatory growth may magnify perceived impact of infection on renal growth
- 3) renal failure
 - incidence of renal failure due to chronic pyelonephritis has fallen significantly
→ from ~20% to <2% now
 - renal scarring can result in **hyperfiltration, concentrating defects, proteinuria, micro-albuminuria, RTA, and defects in FE_{Na} & FE_{Mg}**
→ likely the result of congenital dysplasia
- 4) somatic growth impairment
 - many kids with VUR fall below the normal age-adjusted growth curve
→ especially those with bilateral VUR + some degree of renal damage
 - suppression of pyelonephritis (by either medical prevention or surgical correction) can result in catch-up growth, both in height and weight

How common is reflux nephropathy?

- **direct relationship with grade of VUR** } DOESN'T predict severity of scars
- grade 1-2 } ~5%
 - grade 3 } ~15%
 - grade 4-5 } 25-50%

What factors determine the severity of renal injury w/ VUR?

- 1) presence of UTI } important in evolution of most renal scars
→ high-pressure "water hammer" effect (may cause focal chronic interstitial inflammation and fibrosis)
- 2) grade of VUR } direct relationship b/w grade of VUR and presence of scars
- 3) age of pt } risk of scarring greatest in kids < 1yr
} scars rarely form after age 5
} most scars occur w/ 1st infection
- 4) anatomic considerations } compound papillae more likely to get scars
→ due to R angle of collecting duct
→ usually in poles
- 5) bacterial virulence factors } MRHA, P pili, P blood group ligands (P1 blood group), O antigen, K antigen, siderophores, Lewis (a-b-)
- 6) host susceptibility } degree of preputial and vaginal bacterial colonization
} **regular effective bladder emptying is most important defense**
- 7) inflammatory response to infection } activation of complement, renal ischemia & reperfusion, release of free radicals, microabscesses
- 8) early dx and effective ABx treatment

ASSOCIATED ANOMALIES AND CONDITIONS

What are some of the anomalies/conditions that are associated with VUR?

- 1) UPJO
 - 1-5% incidence of UPJO in kid w/ VUR } UPJO more common w/ higher grades of VUR (5fold)
 - 10-20% incidence of VUR in kid with UPJO } VUR usually of low grade
 - **UPJO is ALWAYS treated before reflux**
- 2) ureteral duplication
 - **VUR is most common abnormality associated with complete ureteral duplication**
 - **VUR most common in LP** } reflux into both poles is less common
 - VUR associated with a duplex system may take longer to resolve but is NOT associated with higher grade or increased risk of scarring
 - if higher grade and in F, might be assoc'd w/ more breakthrough UTIs and scarring
- 3) bladder diverticula
 - paraureteral diverticulum } Hutch tic (more common w/ Ehlers-Danlos, Menkes', etc)
 - } can distort UVJ and cause VUR
 - } can cause obstruction of ureter or even bladder outlet
 - } has no affect on resolution rates of VUR
 - Rx → treatment of VUR, irrespective of Hutch diverticulum
 - when ureter enters the tic directly (not Hutch), management is different
- 4) renal anomalies
 - cardinal renal anomalies associated with VUR include:
 - a) **MCDK** \ **presence of either mandates a VCUG**
 - b) **renal agenesis** } → contralateral VUR seen in 25% of MCKD and
 - c) **horseshoe kidney** / in 30% of renal agenesis
 - most VUR with MCKD resolves, while most VUR with renal agenesis does not resolve
- 5) megacystis-megaureter association
 - get massive ureteral dilatation + thin-walled enlarged bladder
 - non-obstructive } due to regurgitation of urine from severe VUR
 - more common in M } MUST R/O PUV
 - Rx → vesicostomy can temporarily optimize drainage
 - need correction of VUR
- 6) other syndromes
 - VACTERL syndrome (vertebral, anal, cardiac, tracheo-esophageal, renal, limb)
 - CHARGE syndrome (coloboma, heart, atresia choanae, retardation, genital, ear)
 - imperforate anus

List some GU anomalies associated with VUR. }}} "Visa Has Reversed the DUMMIED Charges"

- VACTERL
- Horseshoe kidney
- Renal agenesis (URA)
- Diverticulum (bladder)
- UPJO
- MCDK
- Megacystis-megaureter
- Imperforate anus
- Exstrophy
- Duplex system
- CHARGE

What are the radiologic signs that might suggest the existence of a UPJO in the setting of VUR?

- 1) dilated ureter with little to no filling of renal pelvis
- 2) contrast that does enter pelvis is poorly visualized due to dilution in large pelvic volume
- 3) large pelvis that fails to demonstrate prompt drainage of contrast

What is the significance of VUR during pregnancy?

- presence of active VUR is a RF for pyelonephritis during pregnancy
- previous **hx of pyelo, VUR, and renal scarring** puts mother at **increased risk of infection** during pregnancy, **as well as PIH & pre-eclampsia**
- previous hx of ureteric reimplantation also increases risk of infection during pregnancy
 - **women with HTN and some renal insufficiency are especially at risk**
 - no increased risk of miscarriage

Rx → correction of VUR is recommended prior to pregnancy } especially if HTN or renal insufficiency
 } new trend towards less Rx

What are RFs for pyelonephritis in adult females with VUR?

- presence of pathogenic bacteria
- hx of childhood UTIs
- renal scarring with or without VUR
- chronic renal insufficiency

What are some of the physiologic changes of pregnancy? } AUA Update #5 - 2005

- 1) hematologic
 - 50% increase in plasma volume, 15% increase in RBC volume } decreased Hct
 - 25-40% increase in total blood volume
 - leukocytosis
 - hypercoagulable state } increased factors 7, 8, 10, fibrinogen
 - } decreased fibrinolysis
 - highest risk of DVT during T3 & immediately post-partum
- 2) cardiovascular
 - 30-50% increase in CO by T3
 - ↓'d SVR } progesterone effect
 - ↓'d venous return with large gravid uterus compressing IVC
- 3) respiratory
 - 20% reduction in FRC \ increased risk of rapid
 - 15% increase in O2 consumption / decline in PaO2
- 4) GI
 - GERD and slower gastric emptying } progesterone
 - } gastrin secretion (placenta) lowers gastric pH
 - increased risk of peri-op aspiration
- 5) GU
 - Renal
 - 1) ↑'d renal size } renal length increases approximately 1 cm
 - 2) ↑'d RBF
 - 3) ↑d GFR: 30-50%
 - 4) ↑'d protein excretion
 - 5) ↑'d urine Ca, citrate, and uric acid excretion
 - 6) ↓'d Cr and BUN
 - 7) ↑'d susceptibility to pyelonephritis
 - 8) urine volume increases in upper tract
 - Collecting system
 - 9) hydronephrosis
 - more common on R } left side protected from compression by sigmoid
 - decreased peristalsis during pregnancy
 - most women in 3rd trimester show significant ureteral dilatation (90% in T3)
 - initially due to muscle-relaxing effects of increased progesterone
 - **later due to mechanical compression by enlarging uterus**
 - Bladder & Urethra
 - 10) bladder becomes hyperemic
 - 11) bladder hypertrophy
 - 12) squamous changes of the urethra } d.t. estrogen
 - 13) SUI

NATURAL HISTORY AND MANAGEMENT

How common is spontaneous resolution of VUR?

→ depends on grade of VUR & age at Dx } grade is most important predictor of resolution

- less likely to resolve if higher grade } most grade 1-2 VUR will resolve (80-85%)
 - } ~50% of grade 3 VUR will resolve
 - } very few cases of grade 4-5 VUR will resolve (<25%)
- less likely to resolve if older age at Dx } congenital VUR more likely to resolve and is most prevalent in neonates & young kids
 - } rate of resolution is ~20% per yr
 - } if going to resolve, VUR resolves in first few yrs

What are the principles of management of VUR?

- 1) spontaneous resolution is very common
- 2) high-grade VUR is less likely to resolve spontaneously
- 3) sterile reflux is benign
- 4) extended use of prophylactic ABx is benign
- 5) success rate with surgical correction is very high

What is the recommended treatment of VUR (AUA Guidelines '97)?

→ NO SCARRING AT DIAGNOSIS

- grade 1-2 VUR } initial prophylaxis for all ages
- grade 3-4 VUR } initial prophylaxis if <10yrs old
 - Sx if persistent on f/u & consider initial Sx if >5yrs old + bilateral
 - } immediate Sx if >10yrs of age + bilateral
- grade 5 VUR } initial prophylaxis if <5yrs of age
 - Sx if persistent on f/u & consider initial Sx if 1-5yrs old + unilateral
 - } immediate Sx for all >5yrs old

→ + SCARRING AT DIAGNOSIS

- grade 1-2 VUR } initial prophylaxis for all ages
- grade 3-4 VUR } initial prophylaxis if <5yrs of age
 - Sx if persistent on f/u & consider initial Sx if 1-5yrs old + bilateral
 - } initial prophylaxis if >5yrs + unilateral
 - Sx if persistent
 - } immediate Sx if >5yrs old + bilateral
- grade 5 VUR } immediate surgery for all >1yr of age
 - prophylaxis vs Sx if <1yr of age

→ consider stopping prophylaxis once toilet trained

→ UTIs less common in older boys so can manage older boys differently than older girls

What are the management options for VUR?

- 1) "watchful waiting"/observation } sterile urine + good bladder emptying is essential
 - prophylactic ABx
 - behavioural Rx
 - probiotics
- 2) endoscopic surgery } many different injectables } eg DEFLUX
 - STING injection technique
 - Dublin modification
- 3) open repair } classified according to approach to ureter
 - intravesical, extravesical, combined
 - } also classified based on position of submucosal tunnel in relation to original hiatus
 - suprahialatal, infrahiatal

Which Abx are commonly used for prophylaxis in VUR?

- TMP, amoxicillin } for infants <2months
- } relative hepatic immaturity means infants can't clear sulfa
- Septra/Bactrim, nitrofurantoin } once >2months of age

What are the 2 main causes of breakthrough infections?

- 1) if organism is sensitive, then didn't take meds or dose is too low
- 2) if organism is resistant, then PVR is too high or dose is too high

What is involved in the medical management of VUR?

- 1) continuous low-dose prophylactic antibiotics until resolution of VUR
 - suspensions OD at 1/3 to 1/4 standard therapeutic dose
 - amoxicillin/ampicillin recommended for children up to 6 weeks in age
 - TMP/SMX after 2 months
 - no TMP/SMX prior to 6 weeks of age → kernicterus
 - nitrofurantoin } best suited to minimizing fecal resistance
 - no nitrofurantoin prior to 2 months
 - d/c prophylaxis once VCUG shows resolution
- 2) bladder retraining } improved toilet hygiene & bladder emptying
 - timed voids
 - double voiding
 - proper perineal wiping (front to back)
- 3) elimination of constipation
- 4) anti-cholinergic therapy if needed for bladder dysfunction
- 5) periodic urine cultures q3mo
- 6) yearly radiologic studies (or q18mos)
 - no need for serial DMSA scans unless recurrent bouts of pyelo w/ scarring suspected
 - no need for confirmatory VCUG even if VUR returns } usually not clinically significant

What are the landmark studies that have validated “watchful waiting” for VUR?

- 1) International Reflux Study in Children
 - kids <9yrs of age with high-grade VUR randomized to WW vs corrective open Sx
 - Sx more effective than prophylaxis at reducing (but not eliminating) occurrence of pyelo
 - incidence of UTIs (~40%) and decrease in renal scarring same in both groups
 - untreated voiding dysfunction associated with more UTIs & persistent VUR
- 2) The Birmingham Reflux Study
 - 104 kids randomized to medical vs surgical management of high-grade VUR
 - incidence of scars same in either group

What are the indications to treat adult VUR?

- non-obstructive flank pain
- febrile UTIs
- pyelonephritis
- ?before pregnancy

SURGICAL MANAGEMENT

List indications for cystoscopy prior to surgery for VUR.

- 1) non-visualization of entire urethra on VCUG
- 2) inconclusive radiographic definition of LUT/UUT anatomy
- 3) uncertainty in ureteral location or anomaly
- 4) localization of Hutch diverticulum
- 5) suspected active infection

What are the principles of surgical correction of VUR?

- 1) **r/o secondary VUR**
- 2) always consider **bladder function** pre-operatively
- 3) adequate mobilization of distal ureter **without tension or devascularization**
- 4) creation of **submucosal tunnel** that is generous in caliber & satisfies the Paquin 5:1 ratio of length to width
- 5) attention to anatomic detail to prevent stenosis, angulation, or twisting
→ **entry point** of the ureter into the bladder (hiatus), **direction of submucosal tunnel**, and the **ureteromucosal anastomosis**
- 6) attention to the **muscular backing** of the ureter to achieve effective anti-reflux mechanism
→ **inadequate muscular backing most common cause of failure**
- 7) **gentle handling of the bladder** to reduce post-op hematuria and bladder spasms

What are the indications for anti-reflux surgery for VUR? } } } “SHARP Blade Now”

- Scars (new)
- High grade VUR (grade 4-5) with evidence of scarring
- Associated with congenital abnormalities of the UVJ (eg bladder tics)
- Renal compromise } failure of renal growth or worsening renal function
- Persistent VUR in girls at Puberty
- Breakthrough UTIs despite prophylactic ABx
- Noncompliance with medical mgt

What are the different open surgical techniques used in the management of VUR?

- pre-op cystoscopy
- Pfannenstiel incision made 2cm above symphysis pubis
- a) intravesical**
 - Politano-Leadbetter (suprahiatal tunnel)
 - Glenn-Anderson (infrahiatal tunnel)
 - Cohen Cross-trigonal } **most commonly used intra-vesical reimplantation**
- b) extravesical**
 - Lich-Gregoire (contraindicated if presence of Hutch & not recommended for bilateral VUR)
- c) combined**
 - Paquin technique } extravesical approach to ureter + Politano-Leadbetter intravesical

How successful is open reimplantation for VUR?

- low-grade VUR } almost 100%
- high-grade VUR } 90-95%

What is the post-op evaluation after VUR open surgery?

- should continue ABx until f/u confirms resolution
- low-grade VUR } U/S at 6-12 weeks
 - } no post-op VCUG needed
 - unless dysfunctional voiding, post-op hydronephrosis, or UTIs
- high-grade VUR } U/S + VCUG at 3months

What are the different intravesical techniques for ureteral reimplantation for VUR?

Technique	Hiatus	Ureteral Orifice
Politano-Leadbetter	new (suprahiatal)	same
Glenn-Anderson	same	new (inferior)
Cohen	same	new (superior & contralateral)

What are the advantages & disadvantages of the different techniques for VUR open surgery?

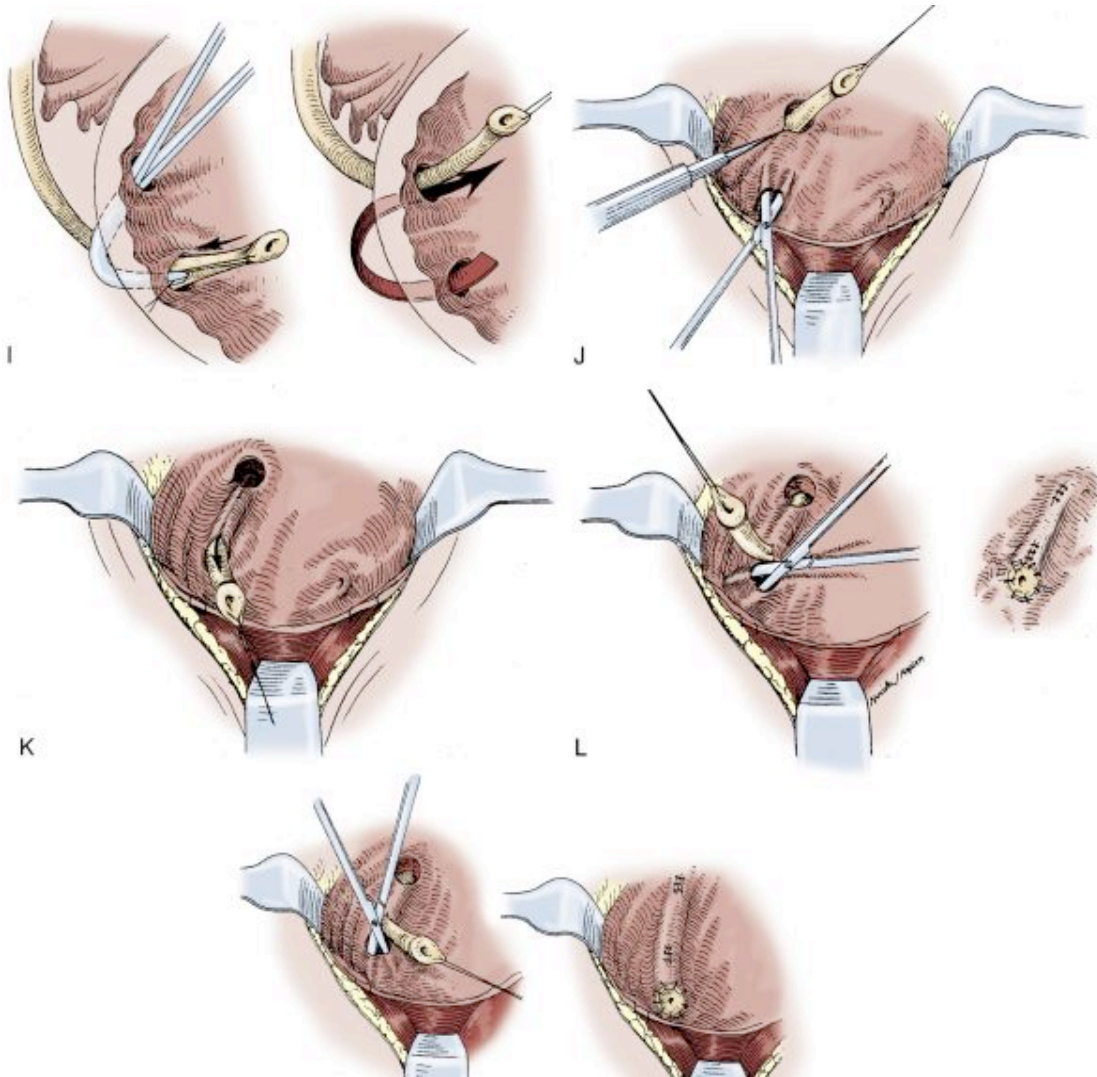
	ADVANTAGES	DISADVANTAGES
→ INTRAVESICAL APPROACH		
Politano-Leadbetter	- long tunnel (good for high grade VUR)	- can get kinking of ureter
Glenn-Anderson	- avoids kinking of ureter	- limited tunnel length - difficult distal anastomosis
Cohen	- long tunnel without difficult distal anastomosis - good for small bladders or thick-walled bladders - rarely get kinks or obstruction - also good if concomitant BN reconstruction indicated	- hard to recannulate the superolateral UO for future studies, treatment, etc
→ EXTRAVESICAL APPROACH		
Lich-Gregoire	- easy - stable submucosal tunnel with good length	- transient urinary retention may be seen in up to 20% (neurologic damage to nerves around distal ureter)
→ COMBINED APPROACH		
Paquin	- stable submucosal tunnel - long submucosal tunnel - ideal for dilated ureters and complex re-do's	

Describe the main steps in setting up the INTRAVESICAL approach to VUR surgery.

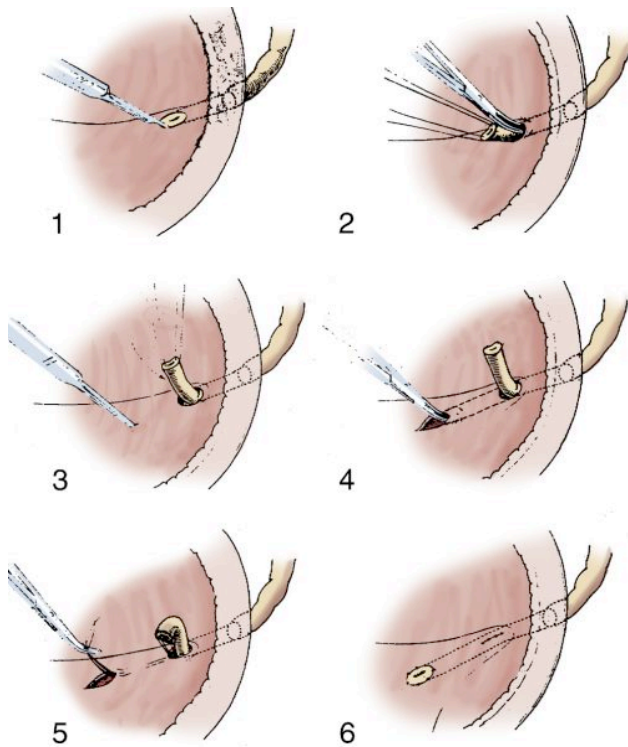
- Pfannenstiel incision
- peritoneum swept off bladder (easier with bladder somewhat full)
- midline incision from dome to ~2cm from BN
- 3-0 Prolene stay sutures placed at lateral edges near dome and at apex near BN
- NS-soaked sponges placed into bladder
- retraction of lateral edges and dome of bladder with minimal trauma
- ureters are cannulated with 3- or 5-Fr feeding tubes and sutured to the bladder mucosa
 - can now inject local + epi in submucosal layer to reduce bleeding
- circumscribing incision made around UO and then ureter is mobilized into bladder
 - best to start at 6-o'clock position with tenotomy scissors
 - don't violate adventitia of ureter (blood supply)
- dissection of ureter is complete once it can reach contralateral bladder wall without tension

Describe the main steps of the ureteromucosal anastomosis for VUR surgery.

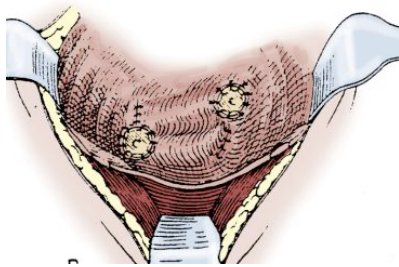
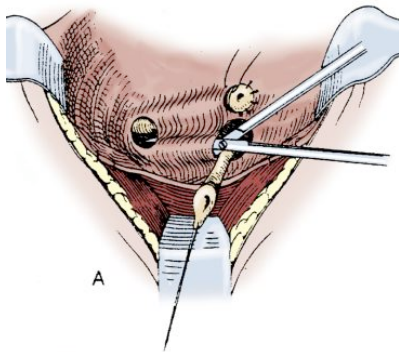
- ureter spatulated at 6-o'clock position
- edges are freshened PRN
- 3 interrupted 5-0 sutures placed close to each other at apex to anchor ureter to trigone
 - grab detrusor and mucosa
- complete anastomosis with interrupted sutures at 2-, 9-, and 12-o'clock positions
- mucosa overlying new hiatus is closed with running 5-0 suture
- bladder closed in 2 layers with 3-0 suture
- Foley placed for 48hrs



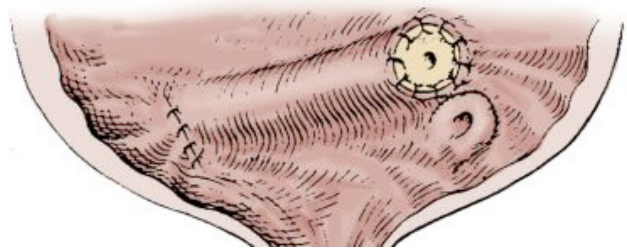
→ INTRAVESICAL APPROACH TO VUR } POLITANO-LEADBETTER (suprahiatal tunnel)
 } new hiatus is made 2.5cm straight above original hiatus



→ INTRAVESICAL APPROACH TO VUR } GLENN-ANDERSON (infrahiatal tunnel)
 } ureter advanced in new tunnel towards the BN



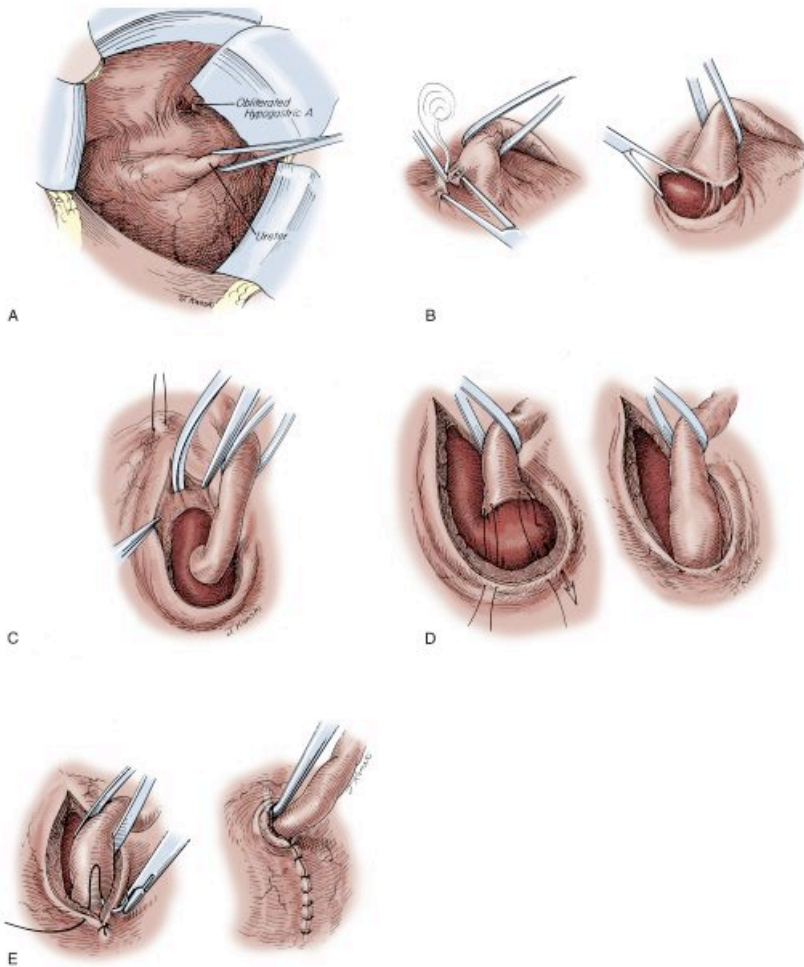
→ INTRAVESICAL APPROACH TO VUR
 - COHEN CROSS-TRIGONAL



→ COHEN TECHNIQUE - UNILATERAL REIMPLANTATION

Describe the main steps in setting up an EXTRAVESICAL approach to VUR surgery.

- Pfannenstiel incision
- dissect peritoneum off dome and lateral wall of bladder
- identify obliterated umbilical artery (branch of internal iliac artery) and divide to facilitate dissection and mobilization of ureter
 - ureter crosses medial to point of origin of obliterated umbilical artery
- ureter dissected down to level of bladder
- course of ureter along posterior wall of bladder is identified and marked for a distance of 5cm
- bladder is filled and retracted medially
- detrusor is incised and new submucosal tunnel is created } uniform mucosal dome bulges out
- detrusor is dissected off mucosa } dissect in proximal-to-distal direction
 - } dissection around ureter left until last
- no need to incise detrusor distal to UO } can cause nerve damage to trigone and lead to higher rates of post-op retention
- after creation of submucosal tunnel, ureter is positioned in new tunnel
- detrusor is closed with 3-0 suture } place most proximal suture first (at new ureteral hiatus) in order to keep tunnel aligned
- +/- Foley for 24-48hrs



→ EXTRAVESICAL APPROACH TO VUR } modified LICH-GREGOIRE
 } no need to do modification above (dissecting distal to UO can injure nerves)

What are the RFs for post-op retention after extravesical VUR repair (Lich-Gregoire)?

- occurs in 20% } usually only transient and Rx'd by Foley or CIC x 1-2 wks
- bilateral reimplantation
- boys
- <3yrs old
- previous voiding dysfunction
- high-grade VUR

COMPLICATIONS OF URETERAL REIMPLANTATION

What are the potential complications following open VUR surgery?

→ EARLY

- 1) persistent VUR } usually resolves
 } more common with high-grade VUR pre-op
- 2) contralateral VUR } more common w/ high-grade VUR & correction of VUR in duplex system
 } may be a synchronous but missed contralateral VUR
 } most resolve
 } **no need for prophylactic B/L reimplant for unilateral VUR**
 } if <5yrs of age, need to re-start prophylactic Abx
- 3) obstruction } mild degree is normal post-op
 } acute obstruction likely due to kinking or twisting, intramural blood clots, or
 extramural compression by submucosal hematoma/edema
 } may need temporary double-J stent or NT
 } usually resolves with time
- 4) urinary retention } seen mainly with **extravesical reimplantations**
- 5) bleeding
- 6) infection

→ LATE

- 1) obstruction } can occur at different locations
 - a) suprahialal } kinking or ischemia
 - b) hiatal } hiatus that is too lateral or anterior leading to "high-reimplant" phenomenon when bladder is full
Rx → may resolve spontaneously but on occasion needs stenting or reimplantation
 - c) tunnel } more common in neurogenic bladder or PUV bladder where its hard to make smooth submucosal tunnel
Rx → balloon dilation or stenting
→ may need reimplantation
 - d) orifice } ischemic stenosis or poor surgical technique
Rx → dilation + stenting
→ endoscopic unroofing (if tunnel long enough)
- 2) recurrent or persistent VUR } very rare for low-grade VUR
 } usually due to inadequate length-to-ureteral diameter ratio (Paquin 5:1 ratio) OR poor muscular backing
 } can also be due to failure to recognize 2° VUR from PUV or neurogenic bladders
 → need to address these issues before reimplant

What are the causes of failure (persistent VUR) after VUR correction?

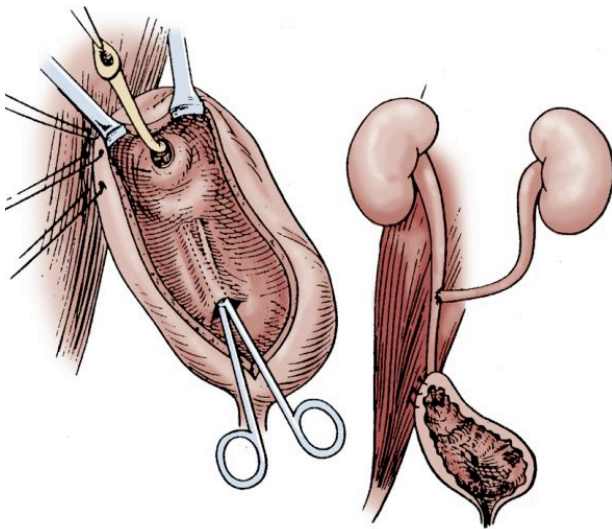
- technical failure } failure to provide adequate muscular backing (**most common**)
 - } inadequate length-to-ureteral diameter ratio (Paquin's 5:1 ratio)
 - } failure to taper dilated ureter
- failure to recognize secondary cause of VUR } PUV
 - } neurogenic bladder
 - } voiding dysfunction
- scarred ureter that can't coapt
- vesicoureteral fistula

List causes of long-term obstruction following reimplantation for VUR.

- ischemia (**most common**)
- angulation at new hiatus
- inadvertent passage of ureter through peritoneum or viscera
- compromise at hiatus or within inadequately developed tunnel

What are the principles of re-do reimplants for VUR?

- dissection of ureter and extensive mobilization needed for adequate tunnel
- **best to use combined extravesical-intravesical approach } Paquin technique**
- excise all ischemic segments of ureter
- preferable to create new hiatus and submucosal tunnel
- use Psoas hitch to gain length } bilateral Psoas hitch not ideal
 - } can perform Psoas hitch on one side and then do a TUU



→ REDO REIMPLANTATION FOR VUR } PSOAS HITCH + TUU

ENDOSCOPIC TREATMENT OF VUR

What are the different endoscopic techniques used in the management of VUR?

→ **r/o possible infection prior to endoscopic treatment**

- 1) classic STING } subureteric Teflon injection (O'Donnell and Puri)
 - } 3.5 to 5 Fr needle inserted (with bevel up) approx. 2-3mm distal to UO
 - } needle advanced in submucosal plane for 4-5mm
 - } goal is to raise a volcano-shaped mound with the UO located at the top
- 2) Dublin modification of STING } needle inserted in submucosal plane but WITHIN intramural ureter

What are the characteristics of the ideal injectable material?

- nontoxic
- stable without migration to other organs
- cause minimal local inflammation
- become well encapsulated by normal fibrous tissue and fibrocytes
- easy to inject
- viscous enough to prevent leakage from puncture site
- durable } maintain injected volume & shape after normal interaction with tissue

What are the different classifications of injectables used for endoscopic correction of VUR?

- 1) particulate vs degradable
 - particulate can migrate
 - degradable may not be durable
- 2) autologous vs non-autologous

How does distant migration of injectable material occur?

- 1) injection causes disruption of small vessels
 - materials gain intravascular access
 - particles <50µm may bypass pulmonary vascular bed and reach systemic circulation
- 2) phagocytosis of injected particles
 - materials <80µm can undergo phagocytosis and be carried into the blood stream

What is the recommended f/u after endoscopic injection for VUR?

- continue Abx for 3 months
- f/u U/S and VCUG at 3 months
 - consider repeat injection at 6 months after initial injection if persistent VUR
- open surgery recommended after 2nd failed injections
 - no additional difficulty after Deflux or Macroplastique (variable after other materials)
 - material removed en bloc before open reimplant

How successful is endoscopic correction of VUR?

- classic STING } ~80% success rate
- **STING + Dublin modification** } **~90-95% success rate**
 - important to note the definition of "success"
 - most studies don't repeat VCUG to determine long-term success
 - goal of injectable agent may be to buy some time for kidney to mature
 - recurrence of VUR later on in life may not be clinically significant

What are the PROS & CONS of the different agents used for endoscopic correction of VUR (includes CHART)?

	PROS	CONS	OTHER
➔ NON-AUTOLOGOUS			
1) PTFE paste	- cheap - viscous	- concern regarding distant migration (40µm) - +++ local inflammation - <u>needs ratched syringe</u>	- NOT USED
2) Bovine collagen	- minimal local inflammation	- poor durability - <u>allergy in 3% of kids</u>	- NOT USED
3) Macroplastique (PDS in Poviodine gel)	- no local inflammation - durable	- can migrate (7% of the particles are <50µm) - needs ratched syringe	- not FDA approved
4) Deflux (dextranomer hyaluronic copolymer)	- no particles are <80µm - easily injected	- not as durable	- preferred by most
5) Coaptite (calcium hydroxyapatite)	- all particles are >75µm - <u>easily injected</u>		
➔ AUTOLOGOUS			
1) chondrocytes	\ /		
2) fat		- not durable	
3) collagen		- need to be harvested	
4) muscle			

LAPAROSCOPY AS APPLIED TO CORRECTION OF VUR

What are the different laparoscopic approaches to VUR correction?

- 1) extravesical reimplantation } most common laparoscopic correction of VUR but technically difficult
- 2) Gil-Vernet procedure } trigonal mucosa incised vertically and the ureters are approximated
into the midline with a single submucosal suture
} difficult and limited success rate (~60%)
- 3) Cohen cross-trigonal reimplantation } transperitoneal vs transvesical
→ can develop pneumovesicum

MEGAURETER

What is a megaureter?

- descriptive term that groups together a spectrum of anomalies assoc'd w/ increased ureteral diameter
→ **any ureter >7-8mm in diameter**
- doesn't imply any particular pathophysiology } dilatation doesn't always mean obstruction

What are the different classifications of megaureter?

- 1) obstructed
 - a) primary } functional obstruction, adynamic segment
 - b) secondary } elevated intravesical pressures (PUVs, bladder dysfunction), retroperitoneal scarring or tumour
- 2) refluxing
 - a) primary } refluxing megaureter, many prune-belly babies
 - b) secondary } BOO, bladder dysfunction
- 3) non-obstructed & non-refluxing
 - a) primary } non-obstructed-non-refluxing (**many neonatal megaureters**)
 - b) secondary } polyuria/diabetes insipidus, infection, post-obstructive dilatation, prune-belly
- 4) refluxing & obstructed (uncommon)

What is the epidemiology of primary megaureter?

- 2-4x more common in boys
- slightly **more common on L side** } **bilateral in 25% of patients (more likely to be 2°)**
- **contralateral kidney is absent or dysplastic in 10-15%**
- no familial predisposition
- prenatal U/S often suggests UVJ obstruction

What is the pathophysiology of megaureter?

- 1) 1° obstructive MGU
 - aperistaltic/adynamic distal ureteral segment that prevents urine flow (functional obstruction)
 - hypoplasia or atrophy of smooth muscle layers
 - excessive collagen } **mostly collagen type I**
→ r/o congenital ureteral strictures and ureteral valves
- 2) 2° obstructive MGU
 - ureter can't expel urine at pressure differential >40 cm H₂O across the UVJ
 - dilatation largely resolves once cause of elevated pressure is relieved (can be permanent)
- 3) 1° and 2° refluxing MGU
 - pressure transmitted to ureter during bladder filling and cyclic voiding
 - excessive collagen } **mostly collagen type III**
 - most prune-belly cases } dilated, tortuous ureter with thickened wall
} collagen replaces normal smooth muscle, especially in distal ureter (greatest dilation seen in distal ureter)
- 4) 1° nonobstructed, non-refluxing MGU
 - **most neonatal cases** } must r/o VUR, UVJO, and secondary causes of dilatation
 - may just be a delay in N segmental maturation of distal ureter (overexpression of TGF-β)
 - may also be due to polyuric state in utero + transient distal obstruction
 - fetal/newborn ureter more compliant than adult ureter } newborn kidneys are protected
- 5) 2° nonobstructed, non-refluxing MGU
 - ureteral dilatation from UTIs due to peristalsis induced by bacterial endotoxins
 - nephropathies can induce polyuric state and overwhelm ureter & lead to progressive dilatation
→ Lithium toxicity, DI, DM, sickle cell nephropathy, psychogenic polydipsia
- 6) refluxing + obstructed MGU (uncommon)
 - dysgenetic distal ureteral segment that doesn't coapt within intramural tunnel but also demonstrates ineffective peristalsis
 - many have ectopic ureter that refluxes when relaxed and is obstructed when taut

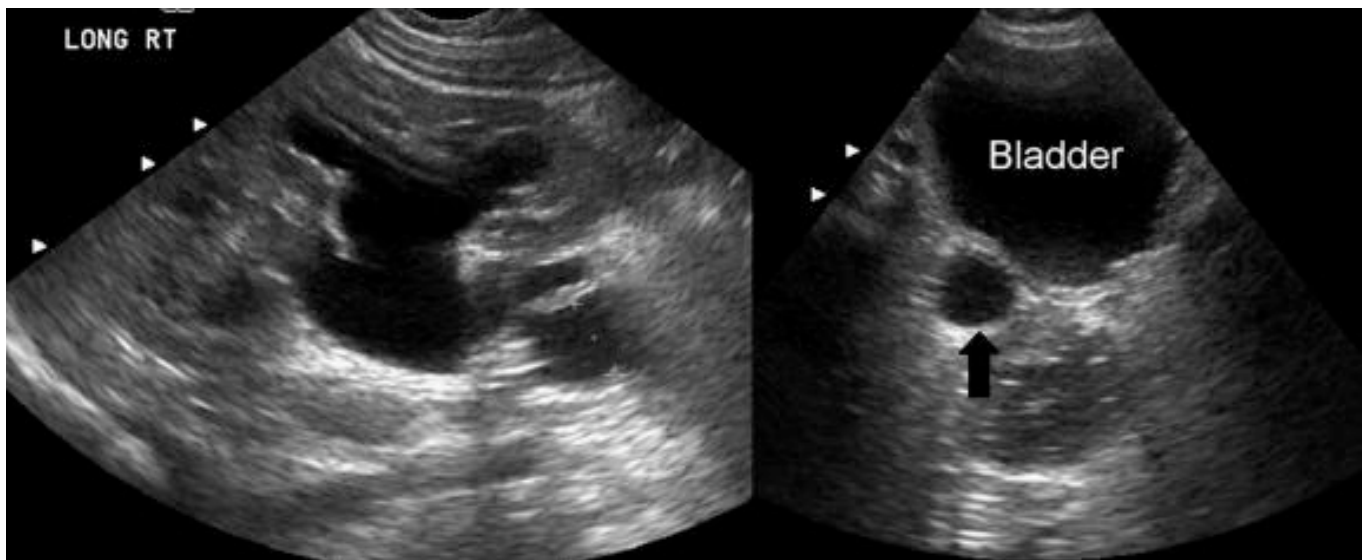
How does primary megaureter usually present?

- **asymptomatic presentation common now with antenatal U/S**
 - UTIs
 - abdo pain
 - hematuria
- rarely present with or progress to renal insufficiency

Evaluation

What imaging studies are used to evaluate possible megaureter?

- 1) U/S } can usually r/o UPJO based on presence of a dilated ureter
 } gives info on parenchyma, collecting system, bladder
 } gives baseline info on degree of dilatation
 } also detects associated anomalies (eg ureterocele)
- 2) VCUG } can r/o VUR
 } also gives info on bladder and urethra
- 3) renal scan } used to judge renal function and estimate degree of obstruction (if present)
 } may be hard to r/o obstruction due to slow wash out times resulting from dilated ureter
 → may need to include ureter in analysis
- 4) MR urography +/- GAD } may replace renal scans
- 5) Whitaker's test } can be used but is quite invasive and needs GA
- 6) cystoscopy + retrograde } best performed at time of surgery



→ ULTRASOUND IMAGES OF MEGAURETER } DILATED RENAL PELVIS + DILATED DISTAL URETER (black arrow)

Management

What are the main indications for correction of MGU?

- increasing dilatation
 - worsening renal function
 - infections
 - no resolution on surveillance
- many cases of antenatally diagnosed MGU will resolve spontaneously

What are the management options for megaureter?

- should treat those with symptoms (UTI, pain, hematuria) different from asymptomatic kids
 - surgery in very young patients is associated with higher complication rates
 - **difficulty is distinguishing 1° obstructed MGU from non-obstructed, non-refluxing MGU**
- 1) primary refluxing MGU
 - treat like VUR
 - prophylactic ABx + serial U/S
 - if no trend toward resolution, worsening renal function, or if infections then consider surgical options (endoscopic vs open)
 - if kid too small for Sx, consider temporizing distal cutaneous loop ureterostomy (if unilateral) or vesicostomy (if bilateral)
 - 2) primary obstructed MGU
 - hard to differentiate from nonobstructed, non-refluxing MGU
 - reimplantation
 - 3) secondary refluxing MGU or secondary obstructed MGU
 - treatment directed at root cause } ablation of PUV, medical mgt of neurogenic bladder
 - some causes can be observed
 - prune-belly syndrome, DI
 - even after correction, some degree of residual dilatation usually persists
 - 4) primary non-obstructed, non-refluxing MGU
 - prophylactic ABx + serial U/S
 - serial renal scans if no clear trend towards improvement
 - if no trend toward resolution, worsening renal function, or if infections then consider surgical options (endoscopic vs open)
 - usually between age 1 and 2 yrs of age
 - if kid too small for Sx, consider temporizing distal cutaneous loop ureterostomy (if unilateral) or vesicostomy (if bilateral)

What are the surgical options used for megaureter?

- surgical goals for reimplantation is similar for non-dilated ureters
- ureteral tailoring is often needed (tapering or plication) to achieve adequate length-to-diameter ratio (Paquin 5:1 ratio) required for successful reimplantation
 - plication or infolding for moderately dilated ureters (preserves vasculature better)
 - excisional tapering usually needed for severely dilated or thickened ureters
- straightening with removal of excess length + proximal revision is usually NOT needed
- **intravesical techniques preferred**
 - cross-trigonal Cohen
 - Politano-Leadbetter (suprahiatal tunnel)
- **extravesical technique may be preferred for very large ureters that need tapering**
 - Lich-Gregoire

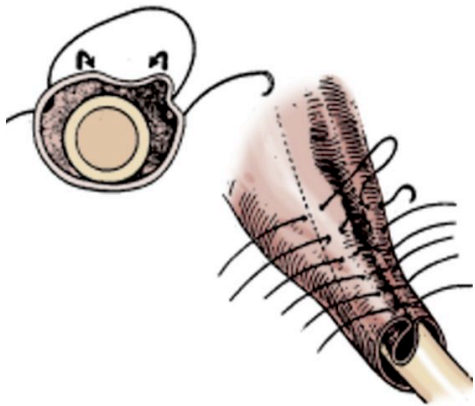
What are the different ways to tailor a megaureter for reimplantation?

→ excisional techniques (better for severely dilated or thickened ureters)

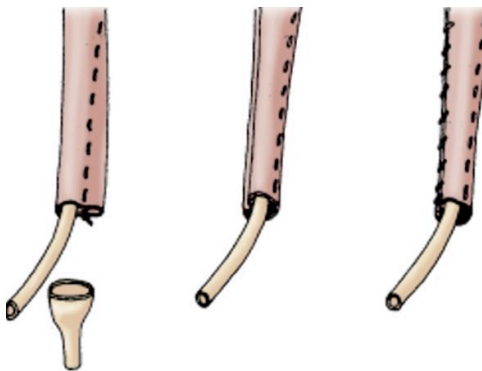
- 1) Hendren tapering } 8Fr feeding tube placed in ureter
 - } Allis clamps placed on medial aspect of ureter to preserve lateral blood supply
 - **pelvic ureter gets blood supply from lateral aspect**
 - abdominal ureter gets blood supply from medial aspect
 - } excess ureter excised
 - } running locking 6-0 PDS used for proximal 2/3 of tapered ureter
 - proximal portion of tailored ureter must remain outside bladder
 - } interrupted sutures used to close distal 1/3 of tapered ureter to allow for any shortening that might be needed

→ plication techniques (better for moderately dilated ureters)

- 2) Starr plication } preserve lateral blood supply
 - } starting proximally, ureter plicated with interrupted 5-0 PDS sutures along clamp impressions in Lembert fashion
- 3) Kalicinski plication } preserve lateral blood supply
 - } two 6-0 PDS sutures placed along clamp impressions, one at proximal end of proposed revision and other at new meatus
 - } ureter divided longitudinally by weaving suture through ureter (creates 2 lumens)
 - } redundant ureter is folded over catheterized lumen



→ STARR PLICATION



→ KALICINSKI PLICATION

Results and Complications

How common are complications after reimplantation for megaureter?

→ **similar to reimplantation for non-dilated ureter BUT HIGHER RATES**

- reflux } ~5% of patients
 - endoscopic injections, open reimplant, TUU (if unilateral), in situ tailoring
- obstruction } usually due to post-op edema
 - } usually resolves in 6-8 weeks (may need temporary NT)
 - } if persists, likely due to ureteral ischemia
 - will need revision } excision of ischemic segment + reimplant

Special Situations

What is the treatment for the dilated duplex ureter?

- salvageable renal function } u-u
 - } ureteropyelostomy
 - } common sheath reimplantation
- no salvageable renal function } heminephrectomy + megaureter excision

Chapter #118 – Prune-Belly Syndrome

GENETICS

What is the genetic background of PBS?

→ **likely NO GENETIC etiology** } **although occasional genetic relations seem present**

→ **mostly sporadic disease**

- most have N karyotype
- more common in twins } but most cases are discordant

List syndromes associated with PBS. }}} “Ed’s Belly Turned Pruned”

- Edward’s syndrome (trisomy 18)
- Beckwith-Wiedemann syndrome
- Turner’s syndrome
- Patau’s syndrome (trisomy 13)

EMBRYOLOGY

What is the embryology behind PBS?

→ 4 different theories } no consensus

- 1) severe posterior urethral obstruction early in utero resulting in severe dilation of GU tract with possible fetal ascites & oligohydramnios
- 2) primary defect in the lateral plate mesoderm
→ precursor of the ureters, bladder, prostate, urethra, and gubernaculum
- 3) intrinsic defect of GU tract leading to ureteral dilation & fetal ascites
- 4) yolk sac defect

CLINICAL FEATURES OF PRUNE-BELLY SYNDROME

What is Prune Belly Syndrome?

→ constellation of anomalies with variable degrees of severity

- aka triad syndrome, Eagle-Barrett syndrome, abdominal musculature syndrome
- **3 major findings (TRIAD)**
 - a) **deficiency of abdominal musculature**
 - b) **bilateral UDT } intra-abdominal**
 - c) **abN GU tract** } variable degrees of renal dysplasia, hydronephrosis, dilated tortuous ureters, enlarged bladder, dilated prostatic urethra
- **75% also have non-GU tract abnormalities** (most common are cardiac, lung & orthopedic)

What is the epidemiology of PBS?

- incidence is 1 in 30K-40K } similar to bladder exstrophy
- **95% in M**
→ females don’t have gonadal anomalies (wall + GU tract only)
- more common in twins, blacks, and kids born to younger mothers

What are the different GU anomalies found in PBS?

- 1) kidney } varies from N to renal dysplasia
 } **renal dysplasia present in 50%**
 → variable degree & laterality
 → see Potter type 2 (parenchymal defect) and 4 (cortical cysts) renal dysplasia
 } **usually get non-obstructive severe hydronephrosis**
 → degree of hydronephrosis DOES NOT CORRELATE with degree of dysplasia
 } calyces relatively well preserved
- 2) ureters } **typically dilated, tortuous, and redundant**
 → ineffective peristalsis
 → distal ureters are more abN than proximal ureters
 → lack of smooth muscle & increased fibrous connective tissue
 } ureters are usually displaced laterally
 } **VUR present in 75%**
 } **can also get UPJO**
 → risk of infection is biggest risk to kidney, not obstruction
- 3) bladder } **smooth-walled, massively enlarged bladder + urachal pseudodiverticulum**
 → “hourglass” bladder on VCUG
 → increased ratio of collagen to muscle fibers in absence of obstruction
 → smooth muscle hypertrophy if obstruction
 → **smooth bladder wall (unlike obstructed bladders)**
 } **patent urachus found in 25-30%**
 } ureteric orifices are displaced laterally and superiorly } may contribute to VUR
 } N compliance bladder on UDS but variable emptying
 → sometimes significant PVR
 } **50% have N voiding pressures, normal flow, and low PVR**
 } **splayed trigone with wide BN**
 → **dilated prostatic urethra**
- 4) prostate and sex organs } **prostatic hypoplasia**
 → get retrograde ejaculation
 } vas & SVs usually atretic or dilated
 } epididymis & rete testis may be poorly attached to testis
- 5) urethra } **20% associated with posterior urethral obstruction**
 → **posterior urethral atresia, PUVs, urethral stenosis, urethral tics, etc**
 } anterior urethra is usually N
 → **can occasionally get anterior urethral atresia or megalourethra**
- 6) testes } **bilateral intra-abdominal UDT**
 } no difference in germ cell counts, Ad spermatogonia, Leydig cells cf to non-PBS UDT
 } **all are infertile** (mixed non-obstructive & obstructive causes)
 } essential to bring down testes for monitoring for testis Ca

What is the DDx of dilated bladder antenatally?

- prune belly syndrome
- PUVs
- obstructing ureterocele
- urethral atresia
- anterior urethral obstruction } eg AUVs, cystic dilatation of Cowper's glands (syringocele)

What are the 2 different types of megalourethra associated with PBS?

- 1) fusiform type } deficient corpus cavernosum + spongiosum
 } entire phallus dilates with voiding
- 2) scaphoid type } deficient spongiosum only
 → preserved glans and corpora cavernosa
 } only ventral urethral dilates with voiding

What other non-GU tract abnormalities are associated with PBS (CHART)?

→ **75% have non-GU tract anomalies**

- 1) abdominal wall defect } thin walled, wrinkled abdominal wall
 - **usually get medial & inferior muscular deficiency**
 - can see intra-abdominal organs in severe cases (skin, fat, peritoneum)
 - } as child grows, abdo wall becomes smooth and pot-bellied
- 2) cardiac } **occurs in ~10%**
 - } **patent ductus arteriosus, ASD, VSD, tetralogy of Fallot**
- 3) pulmonary } can get pulmonary hypoplasia from severe oligo related to renal dysplasia or severe BOO
 - can lead to perinatal mortality
 - } can also get pneumothorax or pneumomediastinum
 - } **significant pulmonary issues in >50% of survivors**
 - can't generate intra-abdominal pressure for coughing, etc
- 4) orthopedic } **occurs in 30-45%**
 - } mostly from compressive effects of oligohydramnios
 - usually unilateral
 - } 25% have talipes equinovarus, 5% hip dysplasia, 5% congenital scoliosis
 - } associated dimples of shoulders and knees
- 5) GI } **found in ~30%**
 - } most GI anomalies from incomplete rotation of midgut
 - **volvulus, atresias, stenosis, splenic torsion**
 - } can also see **omphalocele, gastroschisis, anorectal anomalies, Hirschsprung**
 - } chronic **constipation & acquired megacolon** is an issue
 - can't generate intra-abdominal pressures
- 6) miscellaneous } adrenal cystic dysplasia
 - } splenic torsion

Table 118-1 -- Extragenitourinary Abnormalities

Cardiac	Patent ductus arteriosus
	Ventricular septal defect
	Atrial septal defect
	Tetralogy of Fallot
Pulmonary	Lobar atelectasis
	Pulmonary hypoplasia
	Pneumothorax
	Pneumomediastinum
Gastrointestinal	Intestinal malrotation
	Intestinal atresias or stenosis
	Omphalocele
	Gastroschisis
	Hirschsprung's disease
	Imperforate anus
	Hepatobiliary anomalies
Orthopedic	Pectus excavatum, pectus carinatum
	Scoliosis
	Sacral agenesis (partial)
	Congenital hip subluxation or dislocation
	Genu valgum
	Talipes equinovarus
	Severe leg maldevelopment
Miscellaneous	Splenic torsion
	Adrenal cystic dysplasia

PRESENTATION

What other clinical entities can PBS resemble on prenatal U/S?

- PUVs
- megacystis megaureter syndrome

What are the classic prenatal U/S features suggestive of PBS?

- 1) hydroureteronephrosis
 - 2) distended bladder
 - 3) irregular abdominal wall circumference
- may also see early fetal ascites and abN kidneys

What are the indications for prenatal intervention for PBS?

- no proven benefit in terms of post-natal renal function } degree of hydro doesn't correlate
 - difficult to make in utero Dx of PBS
- only indication may be urethral atresia + progressive oligohydramnios + normal kidney(s)

How does male PBS present in the neonatal period?

- usually Dx is made prenatally
- classic thin, wrinkled abdominal wall suggests Dx
 - cardiac & pulmonary issues may predominate
 - if true BOO (eg urethral atresia), then GU issues may also be urgent } esp. if urachus is not patent
- **20% of boys with PBS die within newborn period**

List the 3 major categories of PBS in the neonatal period - Woodard classification (CHART)?

- 1) **category 1**
 - **renal dysplasia**
 - urethral atresia
 - oligohydramnios
 - **pulmonary hypoplasia**
 - Potter's features

} most die w/in a few days from pulmonary hypoplasia or later from renal failure
Rx → catheter drainage only
- 2) **category 2**
 - full triad features
 - **minimal or unilateral renal dysplasia**
 - **no pulmonary hypoplasia**
 - may progress to renal failure

} variable course from stabilized renal function to progressive azotemia
Rx → controversial
- 3) **category 3**
 - incomplete or mild triad features
 - mild to moderate uropathy
 - **no renal dysplasia**
 - stable renal function
 - **no pulmonary hypoplasia**

} usually some mild GU abnormality but renal function is preserved
Rx → intervention for recurrent UTIs to maintain renal fxn

What is incomplete PBS syndrome?

- **lack typical abdominal wall features** but have GU anomalies & UDT
 - many go on to renal failure (~50%) } often due to delay in Dx
- may present in adulthood w/ renal failure + HTN
- Rx → close observation, monitoring, with selective intervention

How does PBS present in females?

- uncommon } **only 5% of PBS**
- **F's don't have gonadal anomalies** } **abdo wall + GU tract only**
- 40% have anorectal anomalies (similar to males)
- BOO commonly seen
- **40% of girls with PBS die during neonatal period** } **2x mortality rate in M**

EVALUATION AND MANAGEMENT

What is the work-up for a child with PBS?

→ **initial management centres on cardiac & respiratory issues**

- 1) consultation } neonatologist + nephrologists + urologist +/- cardiologist +/- ortho
- 2) lab work } CBC, lytes, BUN, creatinine
 - early creatinine may reflect maternal renal function
 - baseline creatinine <0.7 mg/dL predictive of good renal fxn during childhood
- 3) imaging } immediate CXR
 - r/o pneumothorax, pneumomediastinum, & pulmonary hypoplasia
 - } early U/S
 - r/o GU tract anomalies
 - **urgent urologic Rx only req'd for neonates w/ evidence of BOO**
 - S/P tube
 - } +/- VCUG
 - avoid when possible (infection usually bigger issue than obstruction)
 - **ONLY** if there is renal insufficiency or evidence of BOO
- 4) medications } prophylactic Abx (especially before any instrumentation)
 - to prevent UTIs
- 5) surgical interventions } Cx if no structural penile abn'ities
 - to prevent UTIs

What is the recommended management of PBS based on the Woodard classification?

- category I } bladder drainage
 - } supportive care only
- category II } controversial
 - aggressive surgical intervention VS close monitoring + medical mgt
 - } need individualized evaluation and mgt
 - } MAG3 renal scan at ~4wks to assess differential function & obstruction
 - } infection & progressive renal insufficiency greatest threat to survival and QOL
- category III } usually no intervention needed
 - } early orchidopexy for UDT
 - } serial monitoring of GU tract dilation (U/S) and renal fxn (serum creatinine)

What are the 3 main categories requiring surgical management in PBS?

- 1) GU tract reconstruction
- 2) abdominal wall reconstruction
- 3) orchidopexy

What are the indications for GU tract reconstruction in kids with PBS?

→ **best if delayed until ~3 months old**

- progressive or severe hydronephrosis
- recurrent UTIs
- true obstructive uropathy
- progressive renal failure
- very young and very ill child

What are the surgical options for GU tract reconstruction in kids with PBS?

- 1) cutaneous vesicostomy } procedure of choice when temporary diversion is indicated
 - Blocksom procedure
 - acute renal failure, urinary sepsis, BOO
 - make larger than N stoma for PBS (stenosis common)
 - consider removal of any bladder tics
- 2) supravescical urinary drainage } cutaneous pyelostomy
 - for UPJO, UVJP, or failed distal diversion
- 3) VIU } consider if high PVR, increasing dilation, or VUR + UTIs
 - performed at distal end of prostatic urethra
 - DOES NOT result in incontinence in this population
- 4) reduction cystoplasty } DOESN'T WORK
 - high capacity with PVR seems to recur
 - } only recommended if concurrent excision of large urachal diverticulum or part of a more extensive internal reconstruction
 - CIC +/- mitrofanoff is likely better option
- 5) anterior urethral reconstruction } urethroplasty may be indicated for urethral atresia or megalourethra
- 6) ureteral reconstruction } for recurrent UTIs or progressive upper tract deterioration
 - goal is to reduce urinary stasis

What are the surgical options for UDT in kids with PBS?

- all testes located in abdomen, most commonly on broad mesorchium overlying iliac vessels
- 1) transabdominal orchidopexy
 - **transabdominal orchidopexy at 6months is current approach of choice**
 - placed in scrotum if done before 6 months old (adequate spermatic vessel mobilization)
 - usually combined w/ other Sx's (eg vesicostomy, abdo wall reconstruction)
- 2) 1-stage Fowler-Stephens orchidopexy
- 3) staged Fowler-Stephens orchidopexy
- 4) microvascular autoTx (inferior epigastric)

What are the surgical options for abdominal wall defects in kids with PBS?

- if muscular deficiency is mild, may improve with time
- otherwise, most will not improve
- definite cosmetic benefit
- debatable benefit for bladder, bowel, and lung function
- 3 main techniques include Randolph (transverse cut), Ehrlich (vertical midline cut), and Monfort (vertical elliptical cut)

LONG-TERM OUTLOOK

What factor best predicts future renal function in kids with PBS?

- **nadir serum creatinine } if <0.7 ng/dL**, most will have stable renal fxn during childhood
 - unless compromised by pyelonephritis
- **30% develop CRF during childhood**
- long-term surveillance of GU tract is essential

What is the future fertility status of kids with PBS?

- primary infertility is common
- fertility with ART feasible in those having early successful orchidopexy
 - can retrieve sperm via microTESE

Chapter #119 – Exstrophy-Epispadias Complex

THE EXSTROPHY-EPISPADIAS COMPLEX

What are the 3 main variants of the exstrophy-epispadias complex?

- 1) bladder exstrophy } accounts for >50% of kids born with this complex
- 2) cloacal exstrophy } much more GI involvement
- 3) epispadias

What are the main embryological steps in the development of the cloaca?

- medial ingrowth of mesenchymal tissue reinforces cloacal membrane
- urorectal septum grows distally to meet cloacal membrane, dividing cloaca into bladder anteriorly & rectum posteriorly
- cloacal membrane separated into UG membrane and anal membrane
→ perforation results in UG and anal openings

What is the cause of the exstrophy-epispadias complex?

→ no consensus

a) Marshall-Mueke theory

→ **abN overdevelopment of cloacal membrane prevents medial migration of mesenchymal tissue and later results in abN rupture of cloacal membrane**

→ failure of cloacal membrane to be reinforced by ingrowth of mesoderm results in abN lower abdo wall development

→ depending on extent of defect & stage of development during which rupture of defective cloacal membrane occurs, bladder exstrophy, cloacal exstrophy, or epispadias results

b) Patton-Barry theory

→ **abN development of genital hillocks** distal to N position, with fusion in midline below rather than above cloacal membrane

c) Mildenberger theory

→ **abN caudal insertion of body stalk** results in failure of interposition of mesenchymal tissue in midline

d) Beaudoin theory

→ **lack of rotation of pelvic ring** primordium prevents structures attached to pelvic ring from joining in midline, allowing herniation of bladder to occur

e) Zarabi-Rupani theory

→ involves absence of migration, ascent, or alignment of **allantois** with yolk sac with its persistence at the dome of cloaca

What is the epidemiology of bladder exstrophy?

- uncommon } 1 in 10-50K live births
- **slightly more common in M (2-5x)**
- more common within a given family } 1 in 100
- much more common in offspring of those with exstrophy } 1 in 70
- may involve abN'ity on chromosome 9

What are the RFs for bladder exstrophy? }}} “FAPPY”

- Family history
- use of ART
- higher Parity
- hx of Progesterone in T1 of pregnancy
- Young mother

CLASSIC BLADDER EXSTROPHY

What are the GU features of classic bladder exstrophy?

- 1) Urinary tract
 - bladder mucosa can have hamartomatous polyps, ectopic bowel mucosa, or isolated bowel loop
 - **presence of polyps associated w/ cystitis glandularis**
 - **risk of adenoCa } surveillance cysto**
 - bladder UDS (compliance, stability) can be normal in many after reconstruction
 - **upper tract usually N** } can see **horseshoe kidney, pelvic kidney, solitary kidney, megaureter**
 - ureters take lateral course in pelvis and enter into bladder from inferolateral direction
 - dilated distal ureters
 - **VUR after closure in 100%**
 - **epispadias**
- 2) Genital tract
 - a) males (major reconstructive problem)
 - **short pendular penis (corporal bodies are 50% shorter)**
 - **dorsal chordee**
 - **short urethral plate**
 - flattened scrotum
 - abN prostate that sits posterior to urethra } lower than N PSA values as adult
 - SVs & ejaculatory ducts are N
 - **testes are N (normal fertility)** } commonly retractile
 - b) females
 - **short vagina (<6cm but N caliber)**
 - **cervix found in anterior vaginal wall** } uterine prolapse common as adult
 - stenotic, anteriorly displaced vaginal orifice
 - **bifid clitoris** with divergent labia and mons pubis
 - N fallopian tubes & ovaries

What are the non-GU tract features of classic bladder exstrophy?

- 1) MSK
 - external rotation of posterior aspect of pelvis (~12 degrees)
 - larger SI joint angle (~10 degrees)
 - larger sacrum
 - retroversion of acetabulum
 - external rotation of anterior pelvis (~18 degrees)
 - shortening of pubic rami (30%)
 - **widened pubic symphysis**
 - asymptomatic spinal anomalies (eg MMC, scoliosis, etc)
- 2) abdominal wall
 - **low-set umbilicus**
 - **umbilical hernia (small)**
 - omphalocele (very rare and small)
 - **indirect inguinal hernias (80% of boys, 10% of girls)**
- 3) GI tract
 - short broad perineum
 - anus displaced anteriorly
 - anal incontinence (varying degrees)
 - rectal prolapse (varying degrees) } **if new rectal prolapse after closure, be suspicious of BOO or posterior urethral obstruction**
- 4) other
 - **waddling gait**
 - posteriorly located levator ani (posterior to rectum in ~70%)
 - **N erectile function**

Why are indirect inguinal hernias so common with bladder exstrophy?

- persistent processus vaginalis
- large internal & external inguinal rings
- lack of obliquity of inguinal canal

Which abdominal defects can be closed at the same time of bladder exstrophy closure?

- umbilical hernia
- omphalocele
- indirect inguinal hernia (explore both sides)

What features on antenatal imaging suggest the Dx of bladder exstrophy?

- absence of bladder filling on repeat exams
- lower abdominal wall mass of tissue } increases in size with gestational age
- low-set umbilicus
- widening pubic ramus
- small and abN genitalia
- kidneys usually N

SURGICAL RECONSTRUCTION OF BLADDER EXSTROPHY

What is the immediate post-natal management of a child with bladder exstrophy?

→ **counseling +/- delivery at tertiary care centre if known or suspected antenatally**

- 1) tie off umbilical cord close to abdominal wall
→ don't use clamp, as it can excoriate bladder mucosa
- 2) cover bladder with non-adherent wrap (eg Saran wrap)
→ each time diaper is changed, change wrap after irrigation of bladder mucosa with NS
- 3) transfer to tertiary centre if in community
- 4) abdo U/S + renal scan to assess GU tract
- 5) consult pediatric orthopedics, anesthesia, child psychiatrist
- 6) refer parents for exstrophy support & counseling

What is the main determining factor in deciding on immediate closure?

- bladder quality & functional capacity
- **must be assessed with EUA** } good amount of bladder may be hidden behind fascia
- **bladder capacity >5mL at birth + good elasticity & contractility** can be expected to develop useful function after bladder, abdo wall, and posterior urethral closure

What are the contraindications to primary closure of bladder exstrophy?

- 1) penoscrotal duplication
 - 2) hypoplastic bladder
 - 3) significant bilateral hydronephrosis
 - 4) ectopic bowel within extruded bladder (RELATIVE)
- \ /
let bladder tissue grow
for 4-6 months

What are the principles of the Modern Staged Reconstruction of bladder Exstrophy (MSRE)?

- 1) early bladder, posterior urethral, and abdominal wall closure with osteotomy
- 2) early epispadias repair
- 3) reconstruction of continent BN + ureteric reimplantation
- 4) strict selection criteria for kids suitable for MSRE } MOST IMPORTANT

What are the main stages of the MSRE?

- 1) closure of bladder & abdo wall + urethral closure onto penis + bilateral pelvic osteotomies
 - **newborn period**
 - converts patient into state of complete epispadias + incontinence
 - delayed closure if poor quality bladder template (very small, nondistensible bladder)
 - transverse innominate & vertical iliac osteotomies preferred (anterior approach)
 - gender reassignment (multi-disciplinary decision) is almost never indicated in males
 - prophylactic Abx as 100% have VUR after closure
- 2) epispadias repair (if indicated)
 - **6 months to 1yr of age**
 - prepare with testosterone
- 3) BN reconstruction + VUR correction
 - **4-5 yrs of age** (adequate bladder capacity & child ready for voiding program)
 - gravity cystogram with **capacity >85mL is considered adequate**

What are the advantages of performing pelvic osteotomies at the time of initial closure?

- 1) easy approximation of symphysis with decreased tension on abdo wall closure
- 2) elimination of need for fascial flaps
- 3) placement of urethra deep within pelvic ring } enhances bladder outlet resistance
- 4) brings large pelvic floor muscles near midline } can provide BN support

What are the advantages of the anterior approach to pelvic osteotomies?

- Gearhart technique
- 1) don't need to re-position patient } already supine
- 2) allows placement of external fixator device and intra-fragmentary pins under direct vision
- 3) better cosmetic appearance

When might pelvic osteotomies be avoided?

- **rare scenario } have low threshold to perform osteotomies**
- if patient is <72 hrs old and EUA reveals pubic bones are malleable and able to be brought together easily in midline by medial rotation of greater trochanters

What are the main options if the bladder is not adequate for closure?

- doesn't grow after 4-6 months OR presentation for late primary closure
- 1) cystectomy + non-refluxing colon conduit
- 2) cystectomy + ureterosigmoidostomy
- 3) colon conduit + placement of small bladder inside for later use as posterior urethra
- 4) bladder augmentation + ureteral reimplantation + BN procedure
- 5) continent stoma

OTHER MODERN APPROACHES TO EXSTROPHY RECONSTRUCTION

What are some other methods for primary reconstruction of bladder exstrophy?

- Warsaw approach
- Erlangen approach
- Seattle approach (complete repair)
- combined bladder closure + epispadias repair

What are the 4 key concerns that must be addressed when reconstructing the penis in bladder exstrophy?

- 1) correction of dorsal chordee (orthoplasty)
- 2) urethral reconstruction (urethroplasty)
- 3) glanular reconstruction (glanuloplasty)
- 4) penile skin closure (skin coverage)

Table 119-1 -- Initial Presentation and Management of Exstrophy of the Bladder

Age	Problem	Possible Solution
<i>Initial Presentation</i>		
0-72hr	Classic exstrophy with reasonable capacity and moderate symphyseal separation; long urethral groove; mild dorsal chordee.	I: Midline closure of bladder, fascia, and symphysis to level of posterior urethra; no osteotomy. In very select cases combined bladder closure and epispadias repair.
0-72hr	Above-mentioned findings with short urethra and severe dorsal chordee.	II: Close as in I, adding lengthening of dorsal urethral groove by paraexstrophy skin (cautiously).
0-72hr	Above-mentioned findings with very wide separation of symphysis or late presentation of patient (beyond 72hr up to 1-3yr) for initial treatment.	Osteotomy (combined anterior and vertical iliac) and closure as in I or II.
0-2 wk	Male, penis duplex or extremely short.	Consider female sex of rearing and closure as in I or II (very rare).
0-2 wk	Very small, nondistensible bladder patch.	Prove by examination under anesthesia, then nonoperative expectant treatment awaiting internal or external diversion or delayed closure if bladder plate grows.
<i>Incontinent Period after Initial Closure</i>		
1 mo-4yr	Infection with residual resulting from outlet stenosis.	Urethral dilatation, occasional meatotomy or bladder neck revision.
	Infection, grade III reflux, with pliable outlet resistance.	Continuous antibiotic suppression with plan for early ureteroneocystostomy.
	Partial dehiscence at bladder neck or partial prolapse of bladder (both prevent bladder capacity increase).	Reclosure of bladder neck with osteotomy (with epispadias repair if older than 6 mo of life).
<i>Epispadias Repair Contingence</i>		
6 mo-1yr	Closed bladder with incontinence, normal ultrasound and good penile size and length of urethral groove.	Epispadias repair after preparation with testosterone.
	Epispadias penis, short with severe chordee, before bladder neck reconstruction.	Correction of chordee, lengthening of urethral groove, and epispadias repair, prepare with testosterone.
4-5yr	Epispadias repair, capacity greater than 85 mL, child ready to be dry and be involved in voiding program.	Proceed to bladder neck plasty and ureteroneocystostomy.
4 yr or older	Completed repair of bladder, bladder neck, and epispadias with dry interval but wet pants.	Patience, biofeedback, oxybutynin chloride (Ditropan), imipramine, and time (up to 2yr).
	Above-mentioned problems with marked stress incontinence and good bladder capacity.	Wait—may require bladder neck revision or endoscopic injection or possible artificial sphincter.
	Small-capacity bladder unchanged by time, epispadias repair, or attempted bladder neck reconstruction	Consider augmentation cystoplasty and bladder neck transection/reconstruction; acceptance of intermittent catheterization with abdominal or urethral access may be necessary.
4-7yr	Late presentation of untreated exstrophy, unsuitable for closure.	Consider temporary diversion by colon conduit with plan to undivert to bladder using bladder to form urethra and conduit for augmentation; in patients older than 5yr, artificial sphincter or continent diversion can be considered.
4-7yr	Small closed exstrophy unsuitable for bladder neck reconstruction or augmentation.	Consider permanent external or internal diversion; internal diversion direct by ureterosigmoidostomy or indirect by colocolostomy; evaluate day continence of anal sphincter and nighttime seepage before surgery or continent neobladder.
5-15yr	Closed exstrophy with epispadias repaired with uncontrolled stress or dribbling incontinence.	Consider (1) revision of bladder neck reconstruction, (2) endoscopic injection, (3) augmentation and bladder neck revision, (4) artificial sphincter with omental wrap, and (5) continent diversion.
10-20yr	Closed bladder with inadequate penis.	Consider penile lengthening, urethral reconstruction using free graft, pedicle grafts, and tissue transfer.
10-20yr	Diverted exstrophy with inadequate penis.	As above-mentioned recommendations or penile lengthening without urethral reconstruction (prostatic fistula at base).

MODERN STAGED REPAIR OF EXSTROPHY: OUTCOMES AND RESULTS

What long-term outcomes of bladder exstrophy management are important?

→ **most important factor is successful initial closure**

- urinary continence (achieved in ~70%)
- renal function
- bladder capacity
- cosmesis of epispadias repair

What are the potential complications of primary bladder closure for bladder exstrophy (CHART)?

- bladder dehiscence
- bladder prolapse
- BOO
- bladder stones
- renal stones
- wound dehiscence
- stitch erosion

OTHER EXSTROPHY REPAIRS: OUTCOMES

See text

EXSTROPHY RECONSTRUCTION FAILURES

What are the RFs associated with bladder dehiscence in exstrophy patients?

→ **should wait 6 months before 2nd attempt at closure**

- incomplete mobilization of pelvic diaphragm
- closure under tension
- inadequate pelvic immobilization post-op
- wound infection
- abdominal distension
- urinary tube malfunction (blockage, poor fixation)
- nutritional support
- pain management

What are the potential complications of epispadias repair?

- urethrocutaneous fistula
- urethral strictures
- urethral tortuosity
- loss of glans or corpora
- loss of penile skin
- severe penile scars

CLOACAL EXSTROPHY

What is cloacal exstrophy?

- spectrum of abN'ities } primarily an anterior abdominal wall defect
- **GU anomalies, GI tract anomalies, neurospinal defects, MSK anomalies**
→ GU and MSK anomalies similar to bladder exstrophy but MORE SEVERE

What is the epidemiology of cloacal exstrophy?

- rare } 1 in 200,000 to 1 in 400,000
- relatively **similar incidence between M and F** (maybe slightly more common in M)

What are the GU features of cloacal exstrophy?

- 1) Urinary tract
 - **bladder exstrophy (flanks exstrophied intestines)**
 - upper tract anomalies (40-60%) } **renal agenesis (most common)**
 - } **pelvic kidney (most common)**
 - } MCDK
 - } hydronephrosis
- 2) Genital tract
 - **complete phallic separation**
 - **separation of scrotum**
 - UDT
 - **inguinal hernias**
 - **widely divergent clitoral halves**
 - **Mullerian anomalies** } eg uterine duplication (most common Mullerian anomaly), vaginal duplication, vaginal agenesis, etc
 - infertile males but N fertility in females

What are the other features of cloacal exstrophy?

- 1) MSK defects
 - **wide pubic diastasis**
 - lower limb anomalies (12-65%) } eg **clubfoot**
- 2) GI tract anomalies
 - **exstrophy of terminal ileum between 2 halves of bladder**
 - **imperforate anus**
 - hindgut anomalies (50%) } eg short gut syndrome, malrotation, etc
 - **omphalocele (>90%)**
- 3) neurospinal defects
 - **neurospinal defects (85-100%)** } eg lumbar myelodysplasia, abN peripheral innervation
- 4) other
 - CV anomalies (rare)
 - pulmonary anomalies (rare)

What features on antenatal imaging suggest the Dx of cloacal exstrophy?

- large midline infraumbilical anterior abdominal wall defect
- cystic anterior wall structure
- **omphalocele**
- lumbosacral **MMC**
- absence of bladder filling on repeat exams
- other minor features } **lower limb defects, renal anomalies**, ascites, widening pubic ramus, narrow thorax, hydrocephalus, single umbilical artery

SURGICAL RECONSTRUCTION OF CLOACAL EXSTROPHY

What is the immediate post-natal management of a child with cloacal exstrophy?

- **counseling +/- delivery at tertiary care centre if known or suspected antenatally**
- **consider issue of termination if diagnosed antenatally**
- **medical stabilization is priority**
- 1) tie off umbilical cord close to abdominal wall
 - don't use clamp, as it excoriates bowel & bladder mucosa
- 2) cover bowel & bladder with non-adherent wrap (eg Saran wrap)
 - each time diaper is changed, change wrap after irrigation with NS
- 3) immediate neurosurgery consult if neurospinal abN'ity present
- 4) transfer to tertiary centre if in community
- 5) thorough physical exam to determine associated anatomic defects
- 6) evaluation of genitalia +/- gender assignment discussion } multi-disciplinary decision
- 7) consult pediatric orthopedics, anesthesia, child psychiatrist
- 8) refer parents for exstrophy support & counseling

What are the main aspects of the Modern Staged Functional Reconstruction of Cloacal Exstrophy?

- 1) Functional bladder closure + bowel reconstruction + bilateral pelvic osteotomies
 - neonatal period
 - evaluate anomalies
 - decide whether to proceed with reparative surgery
 - single-stage repair (if few associated anomalies)
 - excision of omphalocele
 - separation of cecal plate from bladder halves
 - bladder closure + urethroplasty +/- genital revision
 - bilateral anterior innominate & vertical iliac osteotomy
 - orchiectomy in M with unreconstructable phallus
 - end ileostomy/colostomy
 - genital revision PRN
 - 2-staged repair
 - as above during 1st stage except the following:
 - delayed bladder closure + urethroplasty
 - osteotomy at time of bladder closure
 - genital revision delayed also
- 2) BN reconstruction + VUR correction
 - 4-5 yrs of age (adequate bladder capacity & child ready for voiding program)
 - eg Young-Dees-Leadbetter for BN and bilateral Cohen for VUR
 - gravity cystogram with capacity >60-85mL is considered adequate
 - +/- augmentation cystoplasty
- 3) vaginal reconstruction
 - augmentation or construction with colon, ileum, of FTSG

LONG-TERM ISSUES IN CLOACAL EXSTROPHY

What are the main long-term issues after initial management of cloacal exstrophy?

- due to near universal survival, focus is on QOL and functional outcomes
- gender reassignment
- urinary continence
- colonic functionalization
- functional genital reconstruction

EPISPADIAS

Male Epispadias

What is the epidemiology of male epispadias?

- **3-5x more common than female epispadias } 1 in 150,000**
- most commonly **assoc'd w/ bladder or cloacal exstrophy** } rare to have isolated M epispadias
- **70% have complete epispadias with incontinence**
→ N urethra replaced by broad mucosal strip on dorsum of penis (extends toward bladder)

What are the features of male epispadias?

- **displaced meatus found in 3 main areas** } on glans, penile shaft, or in penopubic region
→ **penopubic epispadias most common**
→ urinary incontinence more common with proximal defects
- dorsal chordee } found in varying degrees in all cases
- short pendular penis
- widened pubic symphysis } lesser degree than bladder exstrophy

List some anomalies associated with male epispadias?

- mainly genital anomalies } more common & more severe w/ more proximal defects
- **VUR (30-40%)**
- **inguinal hernias**

What are the goals of treatment of male epispadias?

- 1) N urinary control } bladder capacity is most important predictor of future continence
- 2) preservation of upper tracts
- 3) functional penis with acceptable cosmesis

What are the main principles of penile reconstruction in male epispadias?

- release of dorsal chordee (orthoplasty)
- division of suspensory ligaments
- dissection of corpora from attachments to inferior pubic ramus
- lengthening of urethral groove
- lengthening of corpora

What are some different urethral reconstruction techniques used for male epispadias?

- transverse island flap
- complete penile disassembly technique (Bagli et al)
- modified Cantwell-Ransley procedure

Female Epispadias

What is the epidemiology of female epispadias?

- **less common than in males } 1 in 500,000**
- most commonly **assoc'd w/ bladder or cloacal exstrophy** } rare to have isolated F epispadias

What are the features of female epispadias?

- **3 degrees of epispadias** } patulous meatus OR dorsally split along most of urethra
OR complete urethral cleft with incontinence
- bifid clitoris
- poorly developed labia minora
- mons pubis has glabrous skin
- pubic symphysis usually closed
- N vagina and internal genitalia

List some anomalies associated with female epispadias?

- **VUR (30-75%) } more common than in M epispadias**
- thin-walled, small bladder

What are the goals of treatment of female epispadias?

- 1) N urinary control } bladder capacity is most important predictor of future continence
- 2) preservation of upper tracts
- 3) functional external genitalia with acceptable cosmesis

Exstrophy Complex and Variants

What are some of the variants of the exstrophy complex?

- 1) "pseudoxstrophy"
 - characteristic MSK defects of exstrophy WITHOUT major defects in GU tract
 - elongated, low-set umbilicus
 - divergent rectus muscles
 - widened pubic symphysis
- 2) superior vesical fissure variant
 - similar muscular & MSK defects as classic exstrophy
 - superior vesical fistula
 - resembles vesicostomy
 - persistent cloacal membrane ruptures only at uppermost portion
- 3) duplicate exstrophy
 - superior vesical fissure opens but fusion of abdominal wall occurs later on
 - portion of bladder elements (mucosa) remains outside
 - can be continent
 - similar muscular & MSK features
- 4) "covered exstrophy"
 - aka split symphysis variant
 - similar muscular & MSK defects as classic exstrophy
 - no GU abnormality but bladder often visible in subcutaneous position
 - most cases have isolated ectopic bowel segment present on inferior abdominal wall

SEXUAL FUNCTION AND FERTILITY IN THE EXSTROPHY PATIENT

What are the features of exstrophy that concern sexual function?

- males
 - abN ejaculation common } volume & retrograde direction
 - abN semen analysis common
 - ART successful
 - **N libido & erectile function**
 - infertility with cloacal exstrophy
- females
 - many require vaginoplasty before intercourse
 - normal libido & orgasms

What are the obstetrical implications of exstrophy?

- vaginal delivery possible
- cervical & uterine prolapse common after pregnancy

LONG-TERM ADJUSTMENT ISSUES

What is the long-term adjustment of kids with bladder exstrophy?

- clinical psychopathology not the rule
- some tendency toward ↑'d problems with acting out or lack of attainment of age-appropriate adaptive behavior
- early support and counseling important

OTHER

What is the difference between omphalocele & gastroschisis?

→ **omphalocele common in cloacal exstrophy but rare in bladder exstrophy**

OMPHALOCELE	GASTROSCHISIS
<ul style="list-style-type: none">- abN development during wk 7-12- can be located anywhere in midline- abdominal viscera covered in translucent sac (amnion, Wharton jelly, peritoneum) → ruptured in 10%- other structural anomalies common- stable incidence	<ul style="list-style-type: none">- abN development during wk 6-7 (earlier)- always to the R of the umbilical cord- full thickness defect in abdominal wall → no membrane covering bowel loops- other structural anomalies less common- increasing incidence

Chapter #120 – Exstrophy-Epispadias Surgery

What are the important pre-op factors of exstrophy surgery?

- 1) iv ABx } pre- and post-op
- 2) pre-op U/S and renal scan to assess upper tracts (baseline)
- 3) pre-op spinal U/S if any suspicion of MMC (more common in cloacal exstrophy)
- 4) pre-op pelvic CT to assess pubic diastasis

What are the important intra-op factors of exstrophy surgery?

- 1) use of osteotomies
- 2) placement of ureteral stents
- 3) avoidance of abdominal distension
- 4) use of intra-op ABx

What are the important post-op factors of exstrophy surgery?

- 1) post-op immobilization
- 2) post-op ABx
- 3) ureteral stents
- 4) good post-op pain management
- 5) avoidance of abdominal distension
- 6) good nutritional support
- 7) secure fixation of all urinary drainage catheters

- [illegible]

CLASSIFICATION OF BLADDER ANOMALIES

How are bladder anomalies classified?

→ **rarely an isolated finding } usually associated with other congenital anomalies**

1) PRE-NATALLY DETECTED

- a) dilated } obstruction or incomplete emptying (without mechanical obstruction)
 - >7mm during T1
 - no evidence of urine cycling
 - +/- oligohydramnios \ N amniotic fluid & renal
 - +/- increased renal echogenicity / fxn if not obstructed
- b) non-dilated } completely absent or unrecognizable due to incomplete formation
 - usually N amniotic fluid levels
 - must first r/o that fetus as not just emptied bladder
 - must repeat U/S after 15-20 minutes

2) POST-NATALLY DETECTED

- a) urachal abnormalities
- b) bladder diverticulum
- c) bladder duplication
- d) other

What are the most common pre-natally detected bladder anomalies?

- 1) dilated (anatomic or functional obstruction)
 - **urethral anomalies (most common) } PUVs, AUVs, congenital strictures, atresia**
 - external BOO } rectal anomalies, sacrococcygeal teratoma, anterior sacral MMC, pelvic neuroblastoma, obstructing syringocele
 - prune-belly syndrome } PBS can be associated with urethral obstruction (20%)
eg PUVs, urethral atresia, etc
 - neurogenic bladder disease
 - congenital megacystis } massive bilateral VUR with a thin bladder wall
} dilated bladder with poorly developed trigone is from VUR
- 2) non-dilated
 - cloacal exstrophy } split bladder + omphalocele + imperforate anus + spinal defects (MMC)
} rectum communicates with bladder
 - bladder exstrophy } only bladder template on lower abdo wall
} widened pubic symphysis + epispadias (M) + bifid clitoris (F)
+ VUR (100%) +/- BN and sphincter issues
 - bladder hypoplasia } lack of urine storage results in abN capacity bladder
} can be due to severe epispadias, UG sinus anomalies, bilateral renal agenesis/dysplasia, ectopic ureters, etc
 - bladder agenesis } absent bladder + **normal rectum**
} likely from atrophy of cranial part of UG sinus or failure to incorporate mesonephric ducts & ureters into trigone
} associated with neuro, ortho, and other GU anomalies
→ **renal agenesis, absent prostate/SVs/penis/vagina**
} usually **incompatible with life (unless ureters drain ectopically)**

What is the management of congenital megacystis?

→ **NOT due to BN obstruction (ie thin, dilated bladder wall)**

→ **from massive VUR (continuous cycling)**

→ can be associated with hypoperistalsis of the GI tract (microcolon-intestinal hypoperistalsis syndrome)

- mostly in F and usually lethal

- 1) prophylactic Abx
- 2) correction of VUR at 6 months } often restores N voiding dynamics
 - reduction cystoplasty } not usually needed

→ usually don't significantly affect fetal development

→ generally treated with conservative measures or a single surgical intervention

2) bladder diverticulum

4) other (eg nephrogenic adenoma of bladder, bladder hemangioma, etc)

→ urachus is remnant of allantois } found b/w anterior dome of bladder & umbilicus

} middle layer of connective tissue

- surrounded by umbilicovesical fascia } diseases usually remains contained

Without excision, risk of urachal adenocarcinoma increased

} commonly get UTIs, inflamed umbilicus, or de

- } must r/o patent omphalomesenteric duct (eg Meckel tic)

→ drainage if abscess forms

b) urachal cyst (30%) } no connection to bladder or umbilicus (**usually close to bladder**)

} more commonly present in adults

- can get abscess, recurrent UTIs, etc (*S. aureus* common)

} Dx confirmed in U/S

- complete excision of urachal remnant structures

} Dx made on sinogram

Rx → complete excision

- } can get stones or UTIs (if narrow neck)

Rx → partial diverticulectomy if symptomatic

- majority are acquired } caused by infravesical obstruction or iatrogenic after bladder Sx

- uncommon in kids

- usually asymptomatic

- paraureteral diverticula (Hutch) can cause ureteral obstruction or VUR

- large bladder tics can get so big that they block BN or urethra

→ excision of paraureteral tics if assoc'd VUR } spontaneous resolution more common in F

- } reimplant of ureter

→ if acquired bladder tic, must treat obstruction first then reassess

→ Deflux another option for VUR

What is the management of bladder duplication?

- can be complete or incomplete \ **complete duplication in sagittal**
- in coronal or sagittal plane / **plane is most common**
→ **2 urethras if complete duplication**
- in complete duplication, can have one side w/o urethra or one side that has incontinent BN
- **90% are associated with duplication anomalies of external genitalia**
- **40% have duplication anomalies of the lower GI tract**
- VUR, ectopic kidneys, renal dysplasia also common
- Rx → work-up includes karyotype, U/S, IVP, VUDS, genitography, and GI tract imaging
- VCUG and renal scans also helpful
- need to find out as much information on anomalies
- initial goal is renal preservation & prevention of UTIs
- long term goal is achieving continence & reconstructing genitalia

What other bladder anomalies are detected post-natally?

- nephrogenic adenoma of the bladder } rare BENIGN tumour usually found in adults
- } usually a reaction to infection, stones, trauma, Sx
- } 5x more common in F
- Rx → TURBT + long-term prophylactic ABx
- surveillance } 80% recurrence
- eosinophilic cystitis } more common in M
- } presents with dysuria, hematuria, S/P pain, urinary retention
- } Dx made on cysto + Bx
- Rx → TURBT + steroids/antihistamines/Abx
- bladder hemangioma } BENIGN vascular tumours
- } associated with Klippel-Trenaunay syndrome
- Rx → YAG laser ablation

What is the DDx of a umbilical leakage in an infant?

- patent urachus
- external urachal sinus
- omphalitis
- simple granulation of healing stump
- patent vitelline/omphalomesenteric duct
- infected umbilical vessel

What are the 2 types of Hutch diverticulum?

- 1) primary Hutch diverticulum } due to congenitally deficient bladder wall
- found **superolateral to orifice**
- } often in kids with FAS, Ehlers-Danlos, Williams syndrome, Menkes' syndrome, etc
- smooth-walled bladder
- isolated with no other tics found
- intermittent
- found in kids without obstruction
- 2) secondary Hutch diverticulum } acquired
- } due to infravesical obstruction
- found in trabeculated bladders
- one of many tics (always present)
- found in kids with obstruction

Chapter #122 – PUVs and Other Urethral Anomalies

POSTERIOR URETHRAL VALVES (PUV)

What are posterior urethral valves?

- **congenital obstructive membrane** in posterior urethra that impedes antegrade flow of urine
- associated with **thickened bladder wall, elevated BN, & enlarged posterior urethra**
- valve thickness varies from rigid, thick to thin, almost transparent } **no muscle in valve**
- **degree of obstruction varies** } results in variable amounts of damage to the urinary tract
- possibly due to anomalous insertion of mesonephric ducts into primitive fetal cloaca (type 1)
→ inserts too anteriorly

What is the epidemiology of PUVs?

- occurs in 1 in 8,000-25,000 live male births
- accounts for **~10% of urinary obstructions diagnosed in utero**
- may have genetic predisposition
- mortality associated with PUVs has decreased over yrs from ~50% to **5-10% mortality rate**

What is the embryology behind PUVs?

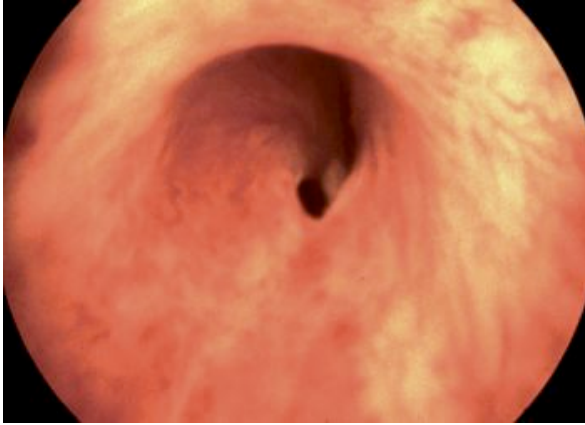
- speculative
- may be related to an abN insertion of the mesonephric ducts into the fetal cloaca
→ type I PUVs
- incomplete dissolution of the UG portion of the cloacal membrane
→ type III PUVs
- valves usually become obstructive during or after the 8th week of life

How are PUVs classified?

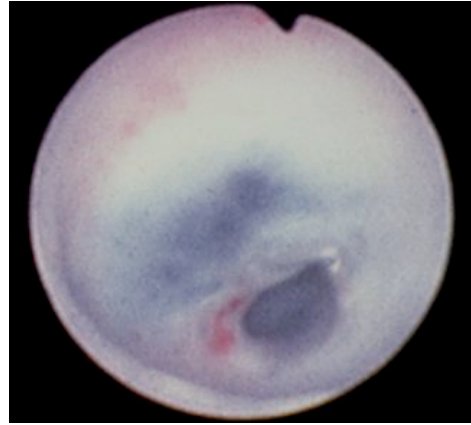
→ **Hugh Hampton Young's classification**

- type I } valve starts at veru & continues anteriorly/distally (**can't see veru on cysto**)
} lack plicae colliculae
} **most common type (95%)**
- type II } valve starts at verumontanum & extends posteriorly towards BN (can see veru)
} NOT OBSTRUCTIVE & result from hypertrophy of muscles of superficial trigone
& prostatic urethra (can be a result of obstructive conditions though eg PUVs)
→ NO LONGER REFERRED TO AS VALVES
- type III } membrane lies transversely across urethra w/ only a small hole near its centre
} distal to veru & can be elongated up to bulbous urethra (can't see veru on cysto)
} accounts for only 5%
} might have worse prognosis

[type IV } seen w/ prune-belly syndrome → flabby unsupported prostate falls in on itself]



→ TYPE I PUV (can't see veru)



→ TYPE III PUV

How do PUVs affect the urinary tract (CHART)?

- kidneys } can develop **obstructive uropathy** from persistent high pressure
 - glomerular injury is partially reversible
 - tubular injury is irreversible (can get nephrogenic DI)
- } can develop **renal dysplasia** from high pressure or abN embryologic development
 - microcystic renal dysplasia mainly in periphery
 - irreversible
- ureter } massively dilated & thickened (damage is usually severe)
 - **all kids have some degree of hydroureteronephrosis**
 - } **presence of VUR in 50-70%**
 - 20-30% resolves after valve ablation
- bladder } **hypertrophy & hyperplasia of detrusor** + increased connective tissue
 - } can develop lifelong bladder problems that can change with age
 - sometimes improve but seldom ever achieve normal function
 - poor sensation, instability, low compliance
 - **incontinence & poor emptying**
- urethra } **distended & thin prostatic urethra**
 - may have larger storage capacity than bladder
 - } **rigid & hypertrophied BN**
 - not obstructive itself but a result of PUV
 - BN function improves after PUV ablated

What are the potential effects of PUVs on other organs (CHART)?

- lung } **pulmonary hypoplasia**
 - may be fatal in newborns } **most common cause of mortality in PUV kids**
 - if infant survives, there are few long-term problems
- kidney } obstructive uropathy
 - glomerular damage usually reversible & improves with initial treatment
 - } renal dysplasia
 - usually irreversible & leads to progressive renal failure and HTN
 - } tubular damage
 - progressive with age and can lead to nephrogenic DI

What factors predispose kids with PUVs to develop renal failure?

- 1) **dysplasia (most important)**
- 2) infections
- 3) persistent obstruction (mechanical or functional)
- 4) HTN
- 5) hyperfiltration of damaged parenchyma
- 6) high-protein diet

What is the VURD syndrome?

- **V**alves, **U**nilateral **R**eflux, and **D**ysplasia
 - dysplastic kidney with reflux in presence of PUVs
 - unilateral VUR most commonly found on L side in setting of PUVs
 - VUR in one kidney allows a pressure “pop-off” valve to protect other kidney
 - found in ~15% of kids with PUV
- initially thought to protect the other kidney without VUR } **doesn't seem to consistently protect long-term kidney function**

Name 5 different “pop-off” mechanisms in kids with PUVs?

- 1) VURD
- 2) patent urachus
- 3) bladder tics
- 4) urinomas
- 5) urinary ascites

Presentation

How does PUV usually present?

- in past, presented with a variety of symptoms & at various ages
 - newborns w/ life-threatening renal or lung issues to toddlers w/ minor voiding dysfxn
- **now, mostly diagnosed with prenatal U/S**
 - oligohydramnios + bilateral hydroureteronephrosis + distended & thickened bladder
- pulmonary hypoplasia } **most severe problem that can lead to mortality**
- renal insufficiency
- urinoma } may have protective effect
- urinary ascites } poorer prognosis
- oligohydramnios + Potter's facies
- deformed limbs
- abdominal masses (distended bladder or hydroureteronephrosis)
- decreased stream } unreliable

How do PUVs present in older kids?

- rare to see now past neonatal period } renal insufficiency seen in 35% of cases
- UTIs
- voiding dysfunction

What other anomalies are associated with PUVs? } } } “P Vowels (AEIOU)”

- **P**runo-belly syndrome
- **A**nemia
- **E**jaculation abN'ities
- Infertility (subfertile – N counts but poor quality)
- **O**steodystrophy
- **U**DT (10%)

Evaluation

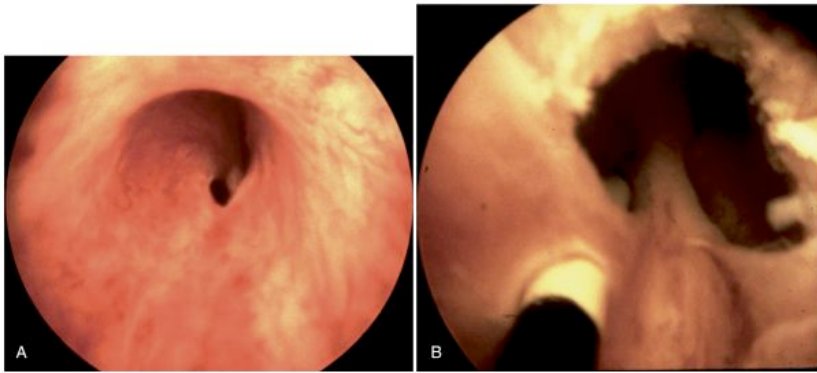
What imaging tests are used to evaluate PUVs?

- U/S } very sensitive for bilateral hydronephrosis but not specific for PUV
 - } PUV may be even harder to Dx if U/S performed at <24 weeks gestation
 - } **classic antenatal U/S findings in PUVs include:**
 - bilateral hydronephrosis
 - distended bladder
 - thickened bladder wall
 - dilated posterior urethra
 - increased renal echogenicity (variable)
 - oligohydramnios (variable)
 - may see “keyhole sign” (variable)
 - findings of neonate same as those on antenatal U/S
- VCUg } **most important test to make Dx of PUV**
 - if Dx is in question, VCUg should be done ASAP
 - } defines anatomy & gross function of bladder, BN, and urethra
 - upper tract findings are not specific to PUVs
 - } **common findings of PUV on VCUg include:**
 - perirenal urinoma
 - severe VUR (in ≥50%)
 - thickened & trabeculated bladder
 - bladder tics
 - elevated hypertrophic BN
 - dilated proximal urethra
 - abrupt urethral caliber change in posterior urethra
 - visible valve in post. urethra
- renal scan } MAG3 ideal (must keep bladder empty with catheter)
 - gives imaging info of parenchyma & collecting system

Management

What is the initial management of PUVs?

- **early VCUg to confirm Dx** } diligent f/u of renal & bladder function is critical
- 1) bladder drainage (permits medical stabilization until decision made about Rx)
 - if PUV suspected, immediate placement of urinary catheter drainage of bladder req'd
 - 3.5 or 5Fr feeding tubes in neonates
 - consider one-shot cystogram to confirm placement (may be hard to get catheter over elevated BN & avoid coiling in dilated prostatic urethra)
- 2) effective NICU support for issues with pulmonary hypoplasia & renal insufficiency
 - ventilatory support, ECMO, dialysis, TPN, BP control, etc
- 3) lab investigations
 - lytes, creatinine, BUN } may take 48hrs to accurately reflect kid's intrinsic renal fxn
 - maternal renal fxn mediated through placenta
- 4) prophylactic ABx
- 5) valve ablation
 - permanent ablation of PUV once stable } **preferred initial surgical treatment**
 - cystoscopic ablation via bugbee electrode, resectoscope, cold knife incision, laser incision, etc
 - goal is not to resect entire valve } higher complication rate (strictures)
 - incision at 12-, 4- or 8-o'clock, or all 3 sites
 - leave catheter in place for 24hrs post incision
- 6) cutaneous vesicostomy
 - **good option if neonate is too small (for instruments) or too sick for PUV ablation**
 - provides adequate drainage & preserves renal function } comparable to primary valve ablation
 - doesn't affect bladder capacity
 - some report that compliance is decreased
- 7) upper tract diversion
 - similar outcomes wrt renal function, somatic growth, etc as primary valve ablation
 - disadvantage of needing further surgery in the future
 - mainly reserved for kids that fail to respond to valve ablation or vesicostomy



→ PUV } BEFORE AND AFTER PUV ABLATION
 } type 1 PUV (most common type) with leaflets distal to verumontanum

What are the causes of persistent hydronephrosis after valve ablation?

- **valve bladder syndrome** } **probably the major cause**
- persistent lower urinary tract obstruction } incomplete ablation or iatrogenic urethral stricture
- distal ureteric or UVJ obstruction
- re-imaging too early
- faulty ureteral musculature
- high urine output (nephrogenic DI)
- VUR (~50% of kids with PUVs and more common on L)

What is the role of upper tract diversion in kids with PUVs?

- in the past, initial management of PUV relied on upper tract diversion with ureterostomy or pyelostomy to effectively decompress upper tracts & control infection
 - kids with high urinary diversion often faced difficult reconstructive issues later in life
 - high diversion produces stomas that present chronic issues with incontinence
- **endoscopic primary valve ablation has made upper tract diversion less attractive**
 - similar wrt control of infection and decompression of upper tracts
 - controversy focused on long-term results } renal & bladder function, somatic growth

What are the indications for upper tract diversion in kids with PUV?

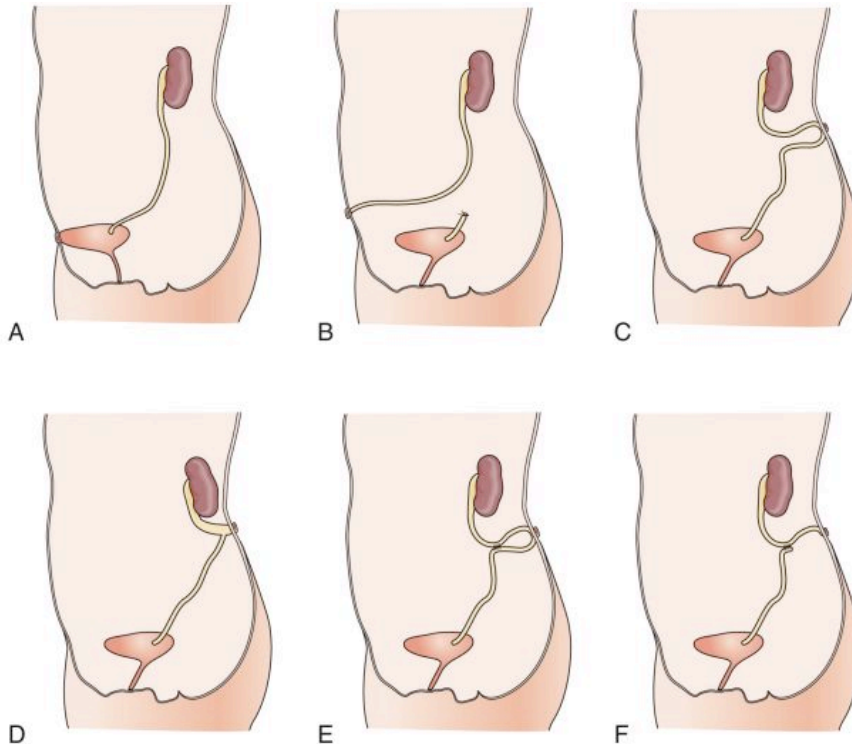
- ensure bladder has been adequately drained
- 1) creatinine (+/-hydronephrosis) that does not improve (>180) after ~10days
- 2) recurrent upper tract infection
- 3) increased PVR after valve ablation

What are the options for upper tract diversion in the management of PUVs?

- distal ureterostomy
- proximal loop ureterostomy
- cutaneous pyelostomy
- ring ureterostomy
- Sober Y ureterostomy

When is the ideal time to undivert a child with PUVs that was managed with upper tract diversion?

- should be delayed until renal & bladder function has been maximized
- if ESRD is likely, can delay until time of renal Tx



- UPPER TRACT DIVERSION FOR PUVs } B – distal ureterostomy
 C – proximal loop ureterostomy
 D – cutaneous pyelostomy
 E – ring ureterostomy
 F – Sober Y ureterostomy

What is the management of VUR associated with PUVs?

- VUR found in 50-70% of kids at time of Dx of PUV } bilateral VUR found in ~30%
 } VUR is secondary to PUV
 } PUVs + VUR assoc'd w/ worse prognosis

→ presence of VUR portends worse survival outcome

- 1) primary valve ablation
 - **VUR resolves in 20-30% after valve ablation } more likely w/ bilateral VUR**
 - usually resolves within several months
- 2) all kids should be on prophylactic ABx
- 3) ensure adequate drainage of bladder with low storage pressure
 - inadequate emptying & high storage pressures may lead to persistent VUR
- 4) if no improvements:
 - repeat VCUG to look for persistent valve remnants
 - UDS to evaluate bladder function
- 5) **surgery only if absolutely indicated**
 - reimplantation of ureters into a valve bladder that has not been adequately rehabilitated is associated with high failure rate & high complication rate
 - mainly limited to the situation in which infections can't be controlled and bladder function is normal and no valve remnants
 - no urgency to remove poorly fxn'ing/dysplastic kidneys UNLESS they lead to recurrent UTIs

What features are predictive of spontaneous VUR resolution after valve ablation for PUVs?

- if associated with a better functioning kidney
- bilateral VUR

What is the management of the hydronephrosis associated with PUVs?

→ almost all kids with PUVs have severe hydronephrosis at time of Dx

- bilateral in ~80%
- secondary to PUV
- 1) primary valve ablation
 - resolves 20-30% of VUR
 - occurs over months
 - resolves non-VUR related hydronephrosis in ~50%
 - occurs fairly rapidly
 - 25% have dilated upper tracts 5-15yrs after successful ablation
 - most of these DO NOT have obstruction at BOO or UVJ
- 2) all kids should be on prophylactic ABx
- 3) imaging studies
 - to r/o obstruction vs VUR

VALVE BLADDER SYNDROME

What is valve bladder syndrome?

→ **chronic condition in PUV kids that develops despite successful valve ablation**

- get intrinsic bladder dysfxn that leads to **deterioration of upper tracts & overflow incontinence**
 - combination of poor sensation + high bladder volumes + poor compliance leads to high storage pressures that prevent adequate drainage of upper tracts
- need VUDS to diagnose valve bladder syndrome

What is the management of bladder dysfunction associated with PUVs?

→ almost all kids with PUVs have some element of chronic bladder dysfunction

→ bladder causes 2 types of long-term problems in kids with PUVs

- 1) interference of upper tract drainage } occurs in infancy (hypercontractile) & in early childhood (poor compliance)
 - 2) incontinence } delayed continence at age 5yrs of age seen in ~80% of PUV kids
- renal tubular damage can develop & lead to nephrogenic DI
- increased urine volumes exacerbate bladder dysfunction
- 3 main types of UDS pattern (overlap in most patients)
- 1) ↓'d compliance/small capacity } more common in infants
 - Rx → anti-cholinergics
 - augmentation cystoplasty if refractory to meds
 - 2) detrusor overactivity } more common in toddlers
 - } get frequency with urge incontinence
 - Rx → anti-cholinergics
 - 3) myogenic failure } usually in older kids (post-pubertal)
 - } incomplete emptying + overflow incontinence
 - Rx → timed voiding, double voiding
 - α-blockers
 - CIC +/- nocturnal catheter

What is the management of glomerular injury & renal insufficiency associated with PUVs?

→ **primary goal is to preserve renal function and maximize renal growth & development**

- get 2 initial glomerular insults } dysplasia + obstructive uropathy
- } dysplasia is the most important because it is irreversible

- 1) ensure no obstruction
- 2) prevent infections
- 3) control HTN

ANTENATAL DIAGNOSIS AND MANAGEMENT

What urologic anomalies should be considered for antenatal intervention?

- PUVs are the only urologic anomaly that may require in utero Rx
- fetal intervention is rare due to the relative lack of evidence that it alters renal development

What is the DDx of bilateral antenatal hydronephrosis?

→ **NORMAL TRANSIENT PHYSIOLOGIC FINDING IS MOST COMMON CAUSE !!!!!**

1) **bilateral VUR (most common pathologic cause of bilateral antenatal hydro)**

2) PUVs

3) bilateral UPJO

4) bilateral primary megaureter

5) PBS (from associated VUR)

6) bilateral duplication with obstruction

7) prolapsing ectopic ureterocele (causes BOO)

8) bilateral multicystic or AD PCKD

→ **UPJO is most common cause of UNILATERAL hydronephrosis**

List the indications & conditions for in utero decompression for obstructive uropathy (CHART)

→ fetal intervention only indicated when life of neonate is at risk

→ also essential that no other life-threatening conditions exist (mainly CV and neurologic)

→ should be a reasonable chance that in utero decompression of the bladder will be beneficial

→ **“BUMKINNES”**

1) presumed **BOO** with severe bilateral hydronephrosis & oligohydramnios

2) Urinary indices are favorable, or serial samplings trending toward normal

- Na <100 (sodium retention)

- Cl <100

- Osm <210 (excretion of free water)

- β 2-microglobulin <10-20

3) **Male** fetus

4) **Karyotype** is N by amnio

5) **Informed** consent

6) **No** systemic anomalies

7) **Noncystic** kidneys (cysts are poor prognostic sign)

8) relatively **Early** onset oligohydramnios (20-25 wks)

9) **Singleton**

What is the current fetal intervention for BOO?

- started at UCSF } double pigtail **vesicoamniotic shunt** (Harrison et al, '82)

- now a Rodeck shunt is placed under U/S guidance

- occasionally need to perform amnioinfusion to permit fetal visualization

- rare cases of intestinal herniation through shunt site

→ ideal time is >20 weeks but before 32 weeks

- oligohydramnios earlier than 20 wks is usually incompatible with life

- early delivery preferable if >32 wks

→ **high risk of complications** } ~40-50%

→ endoscopic fetal intervention has emerged as a new option but likely doesn't provide enough decompression needed in a fetus with severe urinary compromise

PROGNOSTIC INDICATORS OF RENAL FUNCTION

What are the prenatal prognostic variables that predict poor renal function?

- 1) severe oligohydramnios (early is worse)
- 2) early & severe hydronephrosis (present at <24wks with APD \geq 10-15mm)
- 3) renal dysplasia (echogenic kidneys)
- 4) cystic kidneys
- 5) poor fetal urine chemistries
 - Na >100 (inability to retain sodium)
 - Cl >90
 - Osm >210 (inability to retain solutes)
 - β 2-microglobulin >10-20 (elevated in renal dysplasia)
- 6) thick-walled, dilated bladder detected early (in male)
- 7) lack of "pop-off" valve (urinary ascites, VURD, bladder tic, urachal fistula, etc)
 - debatable as to whether this is protective

What are the post-natal prognostic variables that predict poor renal function?

- 1) U/S appearance of kidneys } estimates degree of dysplasia
 - increased echogenicity & loss of corticomedullary differentiation
- 2) age at Dx } older age at Dx may be better
 - } most present antenatally
- 3) presence of VUR } mortality higher with VUR
 - } ~60% if bilateral VUR, ~20% if unilateral VUR, and ~10% if no VUR
- 4) serum chemistries } higher initial creatinine, higher post-drainage creatinine, & higher 1yr nadir
 - associated with worse outcomes
 - nadir <0.7 mg/dL associated with better renal outcomes
- 5) persistence of obstruction

TRANSPLANTATION IN VALVE PATIENTS

What is the most common cause of ESRD in kids?

- **obstructive uropathy is most common cause of ESRD in kids**
 - accounts for ~16% of kids presenting for renal Tx
- PUVs are the most common cause of obstructive uropathy leading to ESRD
 - 30-50% of boys with PUVs will reach ESRD in their lifetime

How successful is renal Tx in boys with PUVs?

- **similar rates of graft survival & renal function**
- **higher rate of urologic complications } ~20%**
 - } urethral strictures, stones, urinary retention
- careful UDS evaluation of bladder function prior to renal Tx is ESSENTIAL
 - may need CIC or augmentation cystoplasty to function safely with new kidney

SUMMARY OF PUV MANAGEMENT

Outline the management of a child w/ PUVs.

- depends on degree of renal failure & the child's age
- 1) all require abdo U/S & VCUG with close follow-up +/- UDS
- 2) older children } endoscopic destruction of valve
- 3) neonate } small transurethral catheter (feeding tube)
 - } antibiotics + IV fluid rehydration
 - } assess renal function after 5-7 days of catheter drainage
 - N/satisfactory renal fxn (Cr < 100) } valve ablation
 - if small urethra } antegrade destruction of valves (via SP tract)
 - } vesicostomy if urethra too small
 - poor renal function after catheter drainage } **controversial**
 - options } valve ablation, vesicostomy, or upper tract diversion
 - } after destruction of valves, follow serum Cr and hydro on U/S
 - } VCUG at age 2/12
- 4) long-term surveillance and care
- 5) transplant if needed

ANTERIOR URETHRAL VALVES

What are anterior urethral valves?

- rare compared to PUVs
- **often occurs in form of urethral diverticulum** } one wall acts as an obstructive “valve”
- usually occurs where there is a defect of the corpus spongiosum
- severity of obstruction, degree of hydro, & incidence of renal failure usually better than PUVs
 - **<5% will develop ESRD**

How do kids with anterior urethral valves present?

- usually presents later in childhood
- UTIs
- straining to void
- incontinence
- ventral mass on penis
- antenatal hydronephrosis

What are the management options for anterior urethral valves?

- primary goal is relief of obstruction
- 1) if too sick or young, temporary cutaneous vesicostomy
- 2) surgical management
 - if small tic or a urethral flap } transurethral incision preferred
 - if large tic } open excision of tic + repair of urethra

CONGENITAL URETHRAL STRICTURE

What are congenital urethral strictures?

- rare anomalies that produce same pathologic problems as PUVs
- occurs in posterior urethra
- leads to oligohydramnios, bilateral hydronephrosis, and distended bladder

What is the management of congenital urethral strictures?

- **cutaneous vesicostomy is management of choice**
 - strictures usually too long to be incised and too tight to be dilated

URETHRAL POLYPS

What are urethral polyps?

- rare anomalies of the male urethra
- usually present with intermittent voiding symptoms } hematuria, dysuria, stranguria
- does not produce extensive damage to urinary tract
- usually occurs in prostatic urethra near BN } may be mobile on a long stalk
- usually Dx'd on VCUG and confirmed on cystoscopy
- benign and can be confused with RMS of prostate
 - usually solitary if benign
 - multiple polyps with extension beyond bladder or prostate suggests RMS

Rx → TUR of polyp

URETHRAL DUPLICATION

What are the different types of urethral duplication?

- rare anomaly
- most occur in same sagittal plane
 - dorsal } N meatus + dorsal chordee + 2nd epispadiac meatus
 - } may have incomplete foreskin dorsally
 - } dorsal epispadiac urethra may be blind ending or extend to bladder
 - } may have widened pubic symphysis similar to epispadias or exstrophy
 - ventral } extremely rare
 - } normal or narrow dorsal urethra + 2nd hypospadiac meatus
 - } ventral hypospadiac urethra may be complete or incomplete (blind-ending)
 - } ventral urethra considered more N b/c it usually passes through BN & EUS
 - rarely occur in same horizontal plane (left and right)
 - this type may be associated with duplicated phallus or complete bladder duplication

What is the management of urethral duplications?

- if free from infection & incontinence } no treatment required
- if recurrent infections and/or incontinent } can fulgurate simple accessory duplicate urethras and allow to scar and close
 - } may need to excise duplicate urethra
- if both urethras are functional and end adjacently } may excise septum to make single meatus
- complex Y fistulas } may require extensive urethroplasties with tissue transfer

MEGALOURETHRA

What is a megalourethra?

- **non-obstructive urethral dilation**
- associated w/ abN development of the corpus spongiosum & corpus cavernosum
- two types:
 - scaphoid } spongiosum is only abN segment
 - fusiform } associated w/ defects in cavernosa
- variant } megameatus intact prepuce (MIP)
 - coronally positioned, wide-mouthed meatus and fully formed foreskin

What abnormality is associated w/ megalourethra?

- prune-belly syndrome } more commonly have N anterior urethra but can have megalourethra or even urethral atresia

Outline the management of the megalourethra.

- cosmetic if upper tracts are N } trim urethra for normal caliber

What is a syringocele?

- cystic dilation of Cowper's gland duct within bulbous urethra
- can also cause urethral obstruction

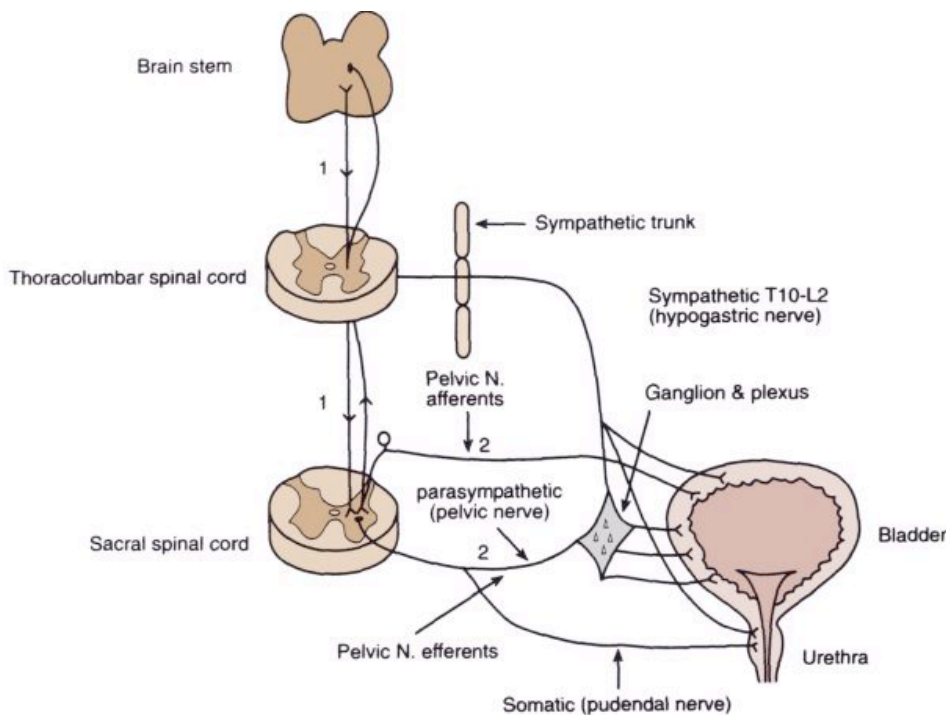
Chapter #123 – Voiding Dysfunction

NON-NEUROPATHIC DYSFUNCTION OF THE LOWER URINARY TRACT

Normal Bladder Function in Infants and Children

What is the innervation of the bladder?

- bladder-sphincter complex involves **both central somatic & autonomic nervous systems** that act via 3 sets of peripheral nerves
- 1) sacral parasympathetics (S2-S4) } pelvic nerves
 - goes through pelvic plexus
- 2) thoracolumbar sympathetics (T10-L2) } hypogastric nerves & sympathetic chain
 - goes through pelvic plexus
- 3) sacral somatic nerves } mainly pudendal nerve (S2-S4)



Describe the initial development of the EUS.

- 1) striated muscle fibers of EUS first appear at ~20 wks } arranged in concentric closed ring
 - 2) posterior splitting of muscle fibers occurs during 1st yr of life } splits in caudal → cranial direction
 - 3) develops into mature omega shape, with fibers absent posteriorly (60% by 1yr of age)
- commonly see detrusor hypercontractility + interrupted voiding during first 2 yrs of life causing some degree of functional BOO
- immature detrusor-sphincter coordination

Name the 5 different sphincteric continence mechanisms in the male urethra?

- 1) internal sphincter (BN)
- 2) prostate
- 3) external sphincter (smooth muscle)
- 4) external sphincter (striated muscle)
- 5) pelvic floor (not true sphincter)

How does infant bladder function differ from bladder function in adults?

→ don't get full adult-like voiding pattern until ~ age 12

- 1) increased voiding frequency as child** } 1x/per hr during first few months
 } 10-15x/day from 6-12 months of age
 } 8-10x/day by age 2-3 yrs
→ frequency decreases with increasing capacity until ~12yrs of age
- 2) higher voiding pressures** } boys higher than girls
 } Pdetmax >100 in boys vs 70-80 in girls
 → mainly seen during 1st yr of life, then decreases with age
- 3) transient detrusor-sphincter discoordination** } interrupted or “staccato” high pressure voiding seen
 → no impairment of overall bladder emptying

What major changes occur in the infant bladder as the child ages?

- 1) increasing capacity } results in decreased frequency & increased voided volumes
→ can also accommodate for N increasing urine production seen
- 2) decreasing voiding pressures
- 3) development of voluntary control over EUS and the detrusor-sphincter complex

What are the 3 main events that must occur for toilet training to be successful?

→ requires an intact nervous system

→ occurs during first 2-3 yrs of life } most are toilet-trained by age 3-4 yrs of age

- 1) progressive increase in functional **storage capacity**
- 2) maturation of voluntary **control over the EUS**
- 3) development of direct volitional **control over the bladder-sphincter complex** } **most important**
 - allows child to voluntarily initiate or inhibit micturition reflex
 - kid becomes aware of sensation of bladder distension and the urge to void

How do you calculate estimated bladder capacity?

- 1) infants
 - capacity (mL) = $38 + [2.5 \times \text{age}(\text{mos})]$
 - capacity (mL) = $7 \times \text{weight}(\text{kg})$
- 2) kids
 - Koff's formula } capacity (mL) = $[\text{Age}(\text{yrs}) + 2] \times 30$
 - Hjalmas' formula } capacity (mL) = $30 + [\text{Age}(\text{yrs}) \times 30]$

Do neonates normally urinate during sleep?

- **micturition does NOT occur during sleep**
 - micturition is not just due to a full bladder + simple spinal cord reflex
 - **involves higher neural centres**
- EEG evidence suggests infants actually awake briefly to urinate in response to distension

What are the different levels of the CNS involved in neurologic control of N micturition?

- cerebral cortex
- thalamus & hypothalamus
- cerebellum
- brain stem (“pontine micturition centre” – Barrington’s nucleus)
- spinal cord (“sacral micturition centre” – Onuf’s nucleus)

What are the major NTs involved in detrusor stimulation?

- acetylcholine
- NE
- prostaglandin substance P
- opioid peptides
- VIP
- neuropeptide Y

Epidemiology & Classification of Non-Neuropathic Bladder-Sphincter Dysfunction in Children

Define “non-neuropathic”.

- based purely on the fact that **NO OBVIOUS and identifiable neurologic lesions are Dx'd**
 - could be neuropathic but lesion has not been identified yet
- certain conditions can behave identically to typical neuropathic bladder-sphincter dysfunctions
 - Ochoa syndrome } urofacial syndrome complex
 - Hinman syndrome

How common is non-neuropathic bladder-sphincter dysfunction?

- 15% of 6yo kids
- likely more common } we only Dx those that present with UTIs, incontinence, etc

How is bladder dysfunction classified?

- 1) abN nervous control
 - congenital CNS malformation } MMC, spina bifida occulta, caudal regression syndrome, tethered cord syndrome
 - developmental disturbances } retardation, dysfunctional voiding, urge syndrome
 - acquired conditions } cerebral palsy, progressive degenerative diseases of CNS assoc'd w/ spasticity, transverse myelitis, MS, vascular malformations, SC trauma
- 2) abN detrusor & sphincter muscle function
 - congenital } muscular dystrophy, neuronal dysplasia (megacolon-megacystis syndrome)
 - acquired } chronic bladder distension, fibrosis of detrusor & bladder wall
- 3) structural abN'ties
 - congenital } bladder exstrophy, epispadias, cloacal anomaly, ureteroceles, PUVs, prune-belly, other urethral anomalies
 - acquired } traumatic stricture or damage to sphincter or urethra
- 4) other unclassified conditions
 - giggle incontinence
 - Hinman syndrome
 - Ochoa syndrome (urofacial syndrome)

What is Functional Classification of Bladder Dysfunction?

→ based on functional state of the bladder-sphincter complex wrt detrusor activity, bladder sensation, bladder compliance and capacity & urethral function (during storage and voiding phases)

1) during FILLING/STORAGE PHASE

- a) detrusor activity
 - N/stable } bladder fills w/o significant rise in Pdet & w/o involuntary ctx's despite provocation (even in newborns)
 - overactive } phasic involuntary detrusor ctx's, which may occur either spontaneously or on provocation
 - } unstable vs hyperreflexic (NOW TERMED IDIOPATHIC vs NEUROGENIC)
 - unstable } ctx's are unrelated to any neurologic disorder
 - } sudden urge that can only be partially suppressed
 - hyperreflexic } overactivity d.t. disturbance of neural control mechanisms
- b) bladder sensation
 - N
 - increased (hypersensitive)
 - reduced (hyposensitive)
 - absent
- c) bladder capacity
 - N
 - high
 - low
- d) bladder compliance
 - N
 - high
 - low

\

 no standardized reference ranges

}

 for compliance in kids

/
- e) urethral function
 - N } +ve closing pressure during filling that decreases just before voiding
 - incompetent } leakage occurs w/o any detrusor contractions despite urethral closure

2) during EMPTYING/VOIDING PHASE

- a) detrusor activity
 - N } voluntarily initiated detrusor contraction
 - can't be voluntarily suppressed until toilet trained
 - underactive } inadequate magnitude and/or duration to result in bladder emptying
 - often seen in over-distended post-obstructive bladder
 - acontractile } due to an abN nervous control
 - complete absence of centrally coordinated contractions
- b) urethral function
 - N } urethra opens to allow bladder emptying
 - obstructive } due to either sphincteric overactivity or mechanical obstruction

What is dysfunctional elimination syndrome (DES)?

→ refers to broad spectrum of functional disturbances that may affect the urinary tract, including that of functional bowel disturbances

- 2 main types of DES

- disorder of filling } OAB, overdistension of bladder or insensate bladder which may be assoc'd w/ fecal impaction or rectal distension with infrequent defecation
 - disorder of emptying } overactive pelvic floor during voiding causing interrupted voiding or incomplete emptying that is assoc'd w/ defecation difficulties due to nonrelaxation of puborectalis & pain on defecation, or even anismus
 - significantly influences outcomes of treating pediatric urologic problems
 - VUR
 - urinary incontinence
 - recurrent UTIs
- DES should be addressed and/or corrected before treatment of urologic problem

Bladder-Sphincter Dysfunction during Bladder Filling

What are the different problems during bladder filling?

- 1) **overactive bladder, urge syndrome, and urgency incontinence**
 - may or may not have urgency incontinence
 - more common in F
 - often see hold maneuvers (eg Vincent's curtsy sign)
 - habitual voluntary pelvic floor ctx may also lead to constipation, fecal soiling
 - leakage usually occurs in afternoon or when preoccupied (during play)
 - often have small bladder capacities
 - delay in CNS maturation
- 2) **functional urinary incontinence**
 - involuntary loss of urine due to failure of control of bladder-sphincter complex
 - SUI is very rare in neurologically N kids
 - normal UDS and urethral resistance
 - amount of leakage usually very small } often associated with older girls that play sports
- 3) **giggle incontinence**
 - involuntary and unpredictable leakage during giggling or laughter
 - usually seen in F
 - may be hereditary
 - larger volumes of leakage cf SUI
 - can almost completely empty bladder
 - UDS usually N
 - may show some occasional detrusor overactivity
 - Rx is very difficult } usually resolves with age/maturity
 - anticholinergics may work occasionally
 - ?centrally mediated - try CNS stimulant (methylphenidate - Ritalin)
 - imipramine

Bladder-Sphincter Dysfunction during Bladder Emptying

What are the different problems during bladder emptying?

- 1) **dysfunctional voiding** } incomplete relaxation or overactivity of pelvic floor during voiding
- 2) **staccato voiding** } bursts of pelvic floor activity during voiding
 - } often have PVR
- 3) **fractionated voiding** } detrusor inactivity that leads to infrequent & incomplete emptying
 - } often get significant PVR & may develop overflow incontinence
- 4) **infrequent voiding/"lazy bladder syndrome"**
 - } more common in F
 - } large PVRs + high capacity + high compliance
 - } absent detrusor ctx's w/ abdominal voiding
 - } can develop overflow incontinence, predisposed to UTIs & often assoc'd w/ constipation
- 3) **Hinman's syndrome** } aka "non-neurogenic neurogenic bladder"
 - } presumed acquired form of bladder-sphincter dysfunction
 - overactive pelvic floor & sphincter during voiding
 - } **bladder decompensation + incontinence + PVRs + UTIs**
 - **most also have bowel dysfunction (constipation, etc)**
 - } clinical & UDS features of neurogenic bladder but NO DEFICITS
 - may actually be some occult neurologic lesion
 - } **2/3 have dilated upper tracts and 50% have VUR**
 - } closely related to Ochoa syndrome (Urofacial syndrome)
 - } management strategy often similar to neurogenic bladder dysfxn
- 5) **post-void dribbling** } likely vaginal voiding and resolves with age
 - } confirmed with VCUG
 - } encourage voiding with thighs apart & leaning forward after voids

What is Ochoa syndrome?

- aka urofacial syndrome } dysfunctional voiding + painful or crying expression during smiling
→ facial neural ganglia is close to pontine micturition centre
- **AR inheritance** with gene on chromosome 10
- **dysfunctional voiding + incontinence + PVRs + UTIs + VUR + upper tract damage + constipation**
- get sustained contraction of EUS during voiding
- **25% have ESRD and 25% have HTN**

Dysfunctional Elimination Syndrome, Constipation, and Bladder Dysfunction

How does abN bowel function affect normal voiding?

- distended rectum } can compress bladder & BN leading to obstruction
- large fecal impaction } may induce detrusor instability, urge syndrome, UTIs, VUR
→ associated with dysfunctional voiding, VUR, recurrent UTIs, and incontinence
→ proper attention to assoc'd bowel dysfxn is key in overall Rx of kids with voiding dysfunction

Relationship between Bladder-Sphincter Dysfunction, VUR, and Recurrent UTIs

What are the most common abN'ities of the lower GU tract found to coexist with VUR?

- 1) **detrusor overactivity (most common UDS finding in kids with VUR)**
- 2) uncoordinated detrusor-sphincter function during voiding (eg DSD)
 - both can worsen VUR and cause upper tract damage
 - VUR may be secondary to bladder dysfunction (especially in girls)
 - boys with VUR usually have higher maximum voiding pressures assoc'd w/ detrusor hypercontractility } may represent a more pronounced form of DSD

How does voiding dysfunction affect the prognosis of VUR?

- delays spontaneous resolution of VUR
- more likely to have recurrent UTIs, even after surgical intervention
- successful Rx of voiding dysfxn improves rate of spontaneous resolution & decreases UTIs

Evaluation of Non-Neuropathic Bladder-Sphincter Dysfunction

What is involved in the work-up of Non-Neuropathic Bladder-Sphincter Dysfunction?

→ often presents after toilet training (incontinence) } can present earlier if UTIs, VUR, etc

1) History

→ r/o symptoms of neurologic or congenital abN'ities

- AM & PM frequency/incontinence
- painful urination
- rectal pain
- vaginal pain/discharge
- penile pain/discharge
- straining to void
- medical and surgical hx } include BP (renal scarring)
- antenatal & perinatal hx } also ask about developmental milestones
- voiding hx (storage & voiding) + voiding diary (intake & outputs)
- bowel hx (encopresis, constipation, fecal impaction, etc)

2) P/E (usually N)

→ r/o signs of neurologic or congenital abN'ities

- palpable bladder
- lumbosacral spine abN'ities
- reduced anal tone
- fixed low urinary specific gravity
- abdominal } palpable bladder, masses
- lower back } asymmetrical gluteal fold, hair tuft, dimpling, tail, vascular malformation, etc
- external genitalia } phimosis, circumcised, labial fusion, meatal location, testes, etc
- rectal exam } fecal impaction, tone, BCR

3) Lab tests

→ not routinely recommended unless presents with complications eg UTIs

- urinalysis } bacteriuria, glucosuria
- serum & urine osmolality } assess renal concentrating ability for nocturnal enuresis

4) Imaging

- U/S } 1st line test to assess upper tracts, BN mobility, bladder wall, and PVR
} may be able to assess pelvic floor muscles and EUS
- VCUG } to r/o VUR
} can also assess bladder wall, urethra, and PVR
- plain film Xray + MRI spine } if suspicious of neurogenic cause

5) UDS

- conventional fill vs natural fill vs ambulatory UDS
- uroflowmetry +/- EMG, CMG (filling), pressure-flow studies (voiding)
- can add video UDS } can assess shape of bladder, BN, urethra, and look for VUR

What are the features suggestive of occult neurogenic dysfunction (RED FLAGS)?

→ symptoms

- AM and PM frequency/incontinence
- painful urination
- rectal pain
- penile pain/discharge
- vaginal pain/discharge
- straining to void

→ signs

- palpable bladder
- lumbosacral spine abN'ities
- reduced anal tone
- fixed low urinary specific gravity

How is uroflowmetry different in kids compared to adults?

- Qmax doesn't correlate with outflow resistance as well as in adults
→ bladder can exert much stronger contraction to counteract increased resistance
- **flow curve is the most important**
 - bell } normal
 - tower shape } common in OAB
 - plateau } obstruction
 - staccato } overactive sphincter
- can add perineal EMG to assess pelvic floor and sphincter during voiding

Management of Non-Neuropathic Bladder-Sphincter Dysfunction

What are the options in the management of non-neuropathic bladder-sphincter dysfxn?

- 1) behaviour modification & standard urotherapy**
 - cognitive, behavioural, & physical therapy with aim to normalize voiding pattern
 - “BEHV” } bladder training (timed voiding, voiding before bed, rewards, etc)
 - } education of parents
 - } habits (changes to drinking & bowel habits, proper wiping habits)
 - } voiding diary
- 2) Pelvic floor muscle training (PFMT) + Biofeedback**
 - builds self-perception of detrusor contractions & pelvic floor relaxation
 - combines uroflowmetry with real-time monitoring } highly effective alone or in combo
- 3) Bowel management**
 - rectal emptying of impacted stool + maintenance of regular soft stools
- 4) Neuromodulation, acupuncture, & other treatment modalities**
 - TENS over S2-S3 to decrease detrusor contractions
 - acupuncture for nocturnal enuresis in S2-S4 segments
- 5) Medications**
 - central or peripherally acting
 - a) anticholinergics (eg oxybutynin) } gold standard for OAB
 - systemic side effects
 - b) α -adrenergic blockers (eg tamsulosin) } if evidence of BN dysfunction
 - c) TCAs (imipramine) } ↑’s urine storage by ↓’ing bladder ctx’s & ↑’ing outlet resistance
 - significant side effects
 - d) β -adrenergic agonists } allows bladder relaxation
 - serious cardiovascular side effects
- 6) CIC**
 - may be needed in kids with decompensated bladders or lazy bladder syndrome
 - can allow for bladder retraining } can improve detrusor contractility
 - no prophylactic ABx required
- 7) surgery**
 - after failed non-surgical management
 - a) botulinum A toxin injection } bladder, sphincter
 - b) bladder augmentation } colon, ileum, stomach

Nocturnal Enuresis

What is the cause of primary nocturnal enuresis?

→ likely multi-factorial

- a) **reduced functional bladder capacity** during sleep
 - reduced nocturnal bladder capacity OR increased urine output at night (eg abN ADH)
 - often also see dysfunctional voiding, bladder overactivity, very high voiding pressures, and marked detrusor hypercontractility
 - **75% have primary BN dysfunction, DSD, or dysfunctional voiding**
 - occasionally there is also an element of nocturnal polyuria
- b) must have a simultaneous **arousal failure** in response to bladder distension
 - arousal inability related to either 1) higher arousal thresholds or 2) presence of spontaneous uninhibited bladder ctx’s
 - most don’t have any symptoms during the day } **although UDS may be abN in >50%**
 - marked detrusor instability is seen only after sleep at night } not during wakeful day
- c) **hereditary**
 - 75% chance if both parents wet during childhood, 45% if one parent
 - AD inheritance with variable penetrance (?chromosome 13)

What is the epidemiology of nocturnal enuresis?

- **majority have primary nocturnal enuresis (85%)**
- **more common in M**
- rule of 15 } 15% of 5yr olds } 15% have encopresis
 } 5% of 10yr olds } 15% become dry each yr
 } 1% of 15yr olds } 15% have initial dry periods (secondary)
 } 15% have daytime symptoms } 15% of non-enuretics have nocturnal awakenings

What is the work-up of nocturnal enuresis?

- 1) history } primary or secondary
 } day & night, or only night
 } characterize voiding & leakage
 → amount, frequency, bother, motivation of child for cure
 → LUTs, curtseying, toilet-training, UTIs, etc
 → **r/o red flags for neurological problem**
 - AM & PM frequency/incontinence
 - painful urination
 - rectal pain
 - vaginal pain/discharge
 - penile pain/discharge
 - straining to void
 - } diet & bowels
 - } developmental hx (premature, LBW, APGARs, neonatal seizures, maternal UTIs, etc)
 - } FMHx (parents), PMHx (neurologic), social hx (stress), meds, allergies
 - } prior evaluation & management
 - 2) P/E } general appearance, vitals (BP)
 } growth chart plot
 } abdominal exam (masses, CVA tenderness, palpable bladder, etc)
 } genital exam (meatus, UDT, hypospadias, testes, labial adhesions, interlabial mass, discharge)
 } neuro & MSK exam (lower back exam for occult signs, anal tone, gait, etc)
 - 3) voiding diary
 - 4) labs } urinalysis, urine C&S, creatinine
 - 5) investigations } uroflow + PVR, U/S, spinal xray
 - } MRI, VCUG if indicated
- | |
|-----------------------------|
| NO INVESTIGATIONS NEEDED IF |
| HEALTHY WITH NO UTIs OR |
| NEURO RED FLAGS |

What is the management of nocturnal enuresis?

→ discourage Rx before age 7 } no success prior to this age

- 1) observation & reassurance
- 2) behaviour modifications } BEHAVE (bladder retraining, education, habits, asked voiding, voiding diary, exercises)
- 3) **wet alarm } most successful treatment option (60-100% success rate)**
 } complications low (buzzer ulcers, high drop out rate)
- 4) meds
 - a) anti-cholinergics } disappointing
 - b) imipramine } cures enuresis in 40-50%
 } improves enuresis in another 10-20%
 } 25mg if <8yrs old, 50mg for older kids
 } S/E's – personality changes, sleep/appetite changes, GI upset, nervousness
 - c) DDAVP } should not be 1st line
 } ideal for overnight camping trips, socially important events, etc
 } 20-40µg for intranasal spray, 200-400µg for oral
 } S/Es – hypoNa and seizures → limit fluids

What are some causes of secondary enuresis?

- following a period of continence
- DM
 - UTI
 - GU abnormalities
 - distal RTA
 - diabetes insipidus

NEUROPATHIC DYSFUNCTION OF THE LOWER URINARY TRACT

Urodynamic Evaluation

What are the main components of the pediatric UDS?

- 1) uroflowmetry
- 2) cystometrogram } **fill rate should be 1/10 capacity per minute (warm NS)**
→ rapid filling can result in falsely low compliance & can mask overactivity
- 3) LPP +/- urethral pressure profile
- 4) pressure-flow studies
- 5) external urethral sphincter EMG } needle electrode vs perineal patch electrodes vs abdominal patch electrodes
- 6) +/- video UDS

What are N voiding pressures in kids?

- **voiding pressures are higher in younger kids than in adults**
- boys = 55-80 cm H₂O
- girls = 30-65 cm H₂O
- adults = <40-60 cm H₂O (lower in women)

What are 4 features on EMG used to confirm intact sacral SC function?

- 1) characteristic waveform of individual motor unit action potentials when pt is relaxed & bladder is empty
- 2) response to bulbocavernosus & anal stimulation, as well as to Crede & Valsalva maneuvers
- 3) activity when patient is asked to voluntarily contract and relax the EUS
- 4) reaction of EUS to filling and emptying of bladder

What are some important findings to look for during UDS?

- uroflowmetry } Is flow rate curve bell shaped, intermittent, or prolonged?
 } What is voided volume?
 } Was there a PVR?
- CMG } Were there any uninhibited contractions?
 } What is the bladder capacity?
 } What were the detrusor filling pressures (compliance) and LPPs?
- pressure-flow studies } Was abdominal pressure used to facilitate the emptying process?
 } Is contraction sustained until voiding is complete on pressure curve?
 } Was there an after-contraction?
- sphincter EMG } Was EMG activity of sphincter quiet throughout the voiding process?

Neurospinal Dysraphisms

When does the spinal canal close?

- formation of spinal cord & vertebral column starts at ~18th day } complete by ~35days

How common is myelodysplasia?

- describes various abN conditions of the vertebral column that affect spinal cord function
- **most common cause of neurogenic bladder dysfunction in kids**
- 1 in 1000 births } decreasing with prenatal screening & folic acid use
 } 0.4mg folic acid od recommended for all (decreases risk by 50%)
 } → 4mg recommended if hx of child with NTDs
- 2-5% chance if already have member of family with spina bifida
- **85% are associated with an Arnold-Chiari malformation**
→ cerebellar tonsils have herniated down through foramen magnum, obstructing 4th ventricle, preventing CSF from entering subarachnoid space (**NEED VP SHUNT**)

What is the functional outcome of spinal dysraphisms?

- neurologic lesion produced depends on what neural elements have protruded
- bony vertebral level & lower extremity dysfunction CAN'T predict neurologic lesion
- **neurologic lesion is a dynamic process } changes seen throughout childhood**

What are the different forms of myelodysplasia?

→ vast majority protrude posteriorly

→ **usually covered by thin covering but may also be leaking CSF } urgent repair necessary**

- 1) occult myelodysplasia
- 2) meningocele } meninges (but no neural elements) extend beyond confines of vertebral canal
- 3) **myelomeningocele** } nerve roots or portions of spinal cord protrude with meningocele
→ **accounts for >90% of all open spinal dysraphic states**
- 4) lipomyelomeningocele } fatty tissue on cord structures and both are extending with protrusion

Where is the most common level of spinal defect?

- | | | |
|--|---|--|
| 1) lumbosacral } most common (~50%) | \ | the higher up the lesion, the more likely it is to be only meningocele, not myelomeningocele |
| 2) lumbar (25%) | | |
| 3) sacral (20%) | | |
| 4) thoracic (5%) | | |
| 5) cervical } least common (2%) | | |

What is involved in the newborn GU assessment of the child with myelodysplasia?

→ before spinal canal closure

- 1) urgent renal U/S (before or after closure)
- 2) early measurement of PVR (normal capacity of newborn is 10-15cc)
- 3) Crede maneuver or CIC performed regularly if unable to void } even before UDS
- 4) urinalysis, urine C&S, serum creatinine
- 5) careful neuro exam of lower extremities

→ after spinal closure } earlier is better

- 1) renal U/S
- 2) renal scan
- 3) VCUG
- 4) UDS } once safe to transfer

What are the benefits of early GU tract assessment in kids with myelodysplasia?

→ **renal U/S, renal scan, VCUG, UDS**

- 1) baseline info used to detect deterioration
- 2) info on condition of the sacral spinal cord and CNS
- 3) helps identify kids at risk for GU tract deterioration due to poor compliance, overactivity, or outflow obstruction from DSD
- 4) helps MD counsel parents on kid's future bladder & sexual function

What are the common GU tract findings on initial evaluation of kids with myelodysplasia?

- **15-20% have an abN GU tract on imaging**
- ~5% have VUR (secondary)
- **10% have N UDS } situation can change as they grow (usually during first 3yrs of life)**
- 60% have bladder contractions } 40% have a non-contractile detrusor
- 40% have intact sacral reflex arc on EMG } 35% have complete loss of sacral cord function

What are the 3 main categories of lower GU tract dynamics detected with myelodysplasia?

- 1) **synergic (~25%)**
 - only 15% have deterioration of GU tract w/in first 3yrs } occurs if conversion to DSD
 - Rx → monitor closely; watch for new DSD
- 2) **DSD +/- poor compliance (40%)**
 - 70% have deterioration of GU tract w/in first 3 yrs
 - Rx → early prophylactic interventions recommended (anti-cholinergics + CIC)
- 3) **complete denervation (35%) } no EUS activity**
 - 25% have deterioration of GU tract w/in first 3 yrs } occurs if increased urethral resistance develops from fibrosis of EUS
 - Rx → monitor closely; watch for BOO

What are the main co-morbidities associated with myelodysplasia?

- bladder dysfunction
- VUR } 2-5% of newborns w/ myelodysplasia
 - almost always secondary VUR
 - if untreated, incidence increases with time
- urinary incontinence
- bowel function } chronic constipation often an issue
- sexuality } fertility worse in M (ED, ejaculation issues, semen quality)
 - } F undergo pubertal changes earlier than N females

What are the pros & cons of early prophylactic Rx for myelodysplasia?

PROS	CONS
<ul style="list-style-type: none">- prevents development of VUR & hydronephrosis- decreases need for bladder augmentation	<ul style="list-style-type: none">- trauma associated with CIC- side effects of anti-cholinergics- 30% risk of meatitis, epididymitis, urethral injury, UTIs- 60-70% on CIC have asymptomatic bacteriuria

What is the management of bladder function in kids with myelodysplasia?

→ depends on risk for GU deterioration

- 1) **behavioural modifications (BEHaV)**
 - Bladder training } timed voiding or CIC (8X per day), voiding prior to bed, watch w/ timing alarm, awake in middle of night to void, proper wiping (front to back), +ve reinforcement (stars or rewards for dryness)
 - Education of parents } what accounts for urine volume, what is normal
 - Habits } lifestyle changes, dietary modification, bowel regime
 - } fluid limitation, avoid irritants/caffeine/EtOH, increase water intake, increase fiber, avoid water in evening
 - Voiding diary
- 2) **PFMT + Biofeedback**
 - pelvic floor physiotherapy & rehabilitation
- 3) **anticholinergics + CIC**
 - **certain groups warrant prophylactic Rx**
 - upper tract deterioration seen in only 8-10% with prophylactic Rx
 - a) all DSD type kids
 - b) evidence of high filling pressures (Pdet >30-40cm H₂O)
 - c) evidence of high voiding pressure (Pdet >80-100cm H₂O)
- 3) **augmentation +/- Mitrofanoff } consider if deterioration/refractory**

List indications for CIC in a child with spina bifida.

- storage problems } DLPP >40 cm H₂O
 - } urinary incontinence
- emptying problems } incomplete emptying (high PVR, areflexia)
 - } inability to void w/ crede (areflexia)
 - } DSD
- other } recurrent UTIs

What are the different options for augmentation cystoplasty?

- for kids **WITHOUT** neurologic deficits, normal sensation in the native urethra can prevent compliance with a routine CIC schedule due to pain/discomfort
- consider **CONTINENT CATHETERIZABLE STOMA** in these kids
 - 1) Ileocystoplasty } 20-40cm segment
 - 2) Ileocecostoplasty } like modified-Indiana
 - appendix can be used as catheterizable conduit
 - removal of ileocecal valve can cause serious diarrhea in some kids
 - 3) Sigmoid cystoplasty
 - 4) Gastrocystoplasty } use of antrum VS use of body
 - mobilized on gastroepiploic artery
 - 5) ureterocystoplasty
 - 6) autoaugmentation ("neo-diverticulum") } improves compliance BUT limited increase in capacity
 - 7) seromuscular enterocystoplasty (coverage of urothelium bulge with bowel)

What are the advantages & disadvantages of the different intestinal segments?

	ADVANTAGES	DISADVANTAGES
STOMACH	<ul style="list-style-type: none"> - less permeable to urinary solutes - has net excretion of H⁺ and CL⁻ - produces less mucus - acidic urine produces less stomal skin irritation - rarely have lyte abN'ities if renal function is normal - lower incidence of bacteriuria - avoids adhesions which are more common in lower abdomen 	<ul style="list-style-type: none"> - can occasionally get severe hypoCL hypoK MET ALKALOSIS - 10% incidence of obstruction - elevated gastrin levels a risk for major intestinal ulcers - decreases stomach volume - high complications of gastric reconstruction (Billroth I) - hematuria-dysuria syndrome
JEJUNUM		<ul style="list-style-type: none"> - severe electrolyte abN'ities such as hypoNa hypoCL hyperK MET ACIDOSIS - Fe deficiency - Ca deficiency
ILEUM	<ul style="list-style-type: none"> - mobile - small diameter - constant blood supply 	<ul style="list-style-type: none"> - can result in anemia (Vit B12 def) - diarrhea (lack of bile salt reabsorption) - fat malabsorption (Vit A, D, E, K) - sometimes has excessive mesentery or very short mesentery - obstruction (10%) more common cf colon - hyperCl hypoK MET ACIDOSIS
COLON	<ul style="list-style-type: none"> - easily mobilized - upper colon safe to use even after pelvic radiation - fewer nutritional problems - lower incidence of bowel obstruction (4%) - easier to make anti-reflux anastomosis via submucosal tunnel 	<ul style="list-style-type: none"> - if ileocecal valve used can result in diarrhea, bacterial colonization of ileum resulting in abN absorption and fluid loss - hyperCl hypoK MET ACIDOSIS (hypoK is more common with colon cf ileum)

List some of the long-term issues after bladder augmentation with bowel } } } “G-DIVERSIONS”

→ metabolic

- 1) **Growth retardation**
- 2) **Drug metabolism abnormalities**
- 3) **Infections (UTIs)**
- 4) **Vitamin B12 deficiency**
- 5) **Electrolyte abnormalities**
- 6) **Renal failure**
- 7) **Stones**
- 8) **Intestinal problems**
- 9) **Osteomalacia**
- 10) **Neoplasms**
- 11) **Sensorium alterations**

→ mechanical

- bowel anastomotic leak
- SBO
- fistula
- atonic bladder
- delayed spontaneous bladder perforation +/- fistula
- refractory poor compliance/uninhibited contractions

What is the management of VUR in kids with myelodysplasia?

→ VUR resolves in 30-50% if managed properly

→ avoid Crede voiding

- 1) **prophylactic Abx alone** } if grade 1-3 VUR + no compliance/BOO
- 2) **CIC + anticholinergics + Abx** } if high PVR or grade 4-5 VUR or poor compliance/BOO
- 3) anti-reflux surgery } indications for anti-reflux surgery same as in kids with N bladder function
 - Deflux injection \ must ensure complete
 - reimplantation / bladder emptying
- 4) vesicostomy rarely indicated

What are the indications for ANTI-REFLUX SURGERY in kids with myelodysplasia?

→ **same as in kids with N bladder function** } **must ensure complete bladder emptying**

→ “SHARP Blade Now”

- Scars (new)
 - High grade VUR (grade 4-5) with evidence of scarring
 - Associated with congenital abnormalities of the UVJ (eg bladder tics)
 - Renal compromise } failure of renal growth or worsening renal function
 - Persistent VUR in girls at Puberty
 - Breakthrough UTIs despite prophylactic ABx
 - Noncompliance with medical mgt
- persistent hydroureteronephrosis despite effective bladder emptying and lowering of intravesical pressures
- presence of VUR in any kid undergoing surgery to increase bladder outlet resistance

What are the indications for VESICOSTOMY in kids with myelodysplasia?

- 1) VUR so severe that CIC + anticholinergics fail to improve upper tract drainage
- 2) parents can't adapt to CIC
- 3) if not good candidate for augmentation cystoplasty

What is the management of incontinence in kids with myelodysplasia?

- 1) **CIC + anticholinergics**
- 2) botulinum toxin A bladder injections
- 3) add α -agonist if UDS shows inadequate urethral resistance (phenylpropanolamine)
- 4) **with failure of meds, consider surgery** } **must ensure low bladder pressures**
 - a) BN injections } Deflux, collagen
 - b) BN procedures } reconstruction (Young-Dees, Leadbetter, Salle), sling, AUS
 - c) BN closure + diversion +/- augment } mitrofanoff, Monti, etc
 - d) augmentation } bowel segment, auto-augment

List contraindications to AUS insertion in spina bifida children.

- DSD
- high storage pressures (>40 cm H₂O)
- overactivity at low volume

What is the management of bowel function in kids with myelodysplasia?

- constipation is often chronic difficult problem
- fecal incontinence unpredictable } NOT associated w/ achieving urinary continence
- 1) **dietary changes**
- 2) **bowel meds (laxatives, suppositories, enemas)**
- 3) **manual evacuation**
- 4) **Malone's antegrade continence enema (MACE) via appendix or cecostomy tube**
- 5) **psychologic counseling, support groups**

What is the recommended surveillance of a kid with myelodysplasia?

- 1) intact-synergic
 - q4month PVR
 - q1yr U/S & UDS
 - 2) intact DSD
 - q1yr U/S & UDS
 - q1yr VCUG (if known hypertonicity or VUR)
 - 3) partial denervation
 - q4month PVR
 - q1yr U/S & UDS
 - q1yr VCUG (if known hypertonicity or VUR)
 - 4) complete denervation
 - q6month PVR
 - q1yr U/S & UDS
- UDS yearly until ~5yrs of age } consider MRI spine if any consistent changes

What are the common causes of new voiding symptoms in kids w/ myelodysplasia?

- | | | |
|---|---|---|
| 1) tethered cord | \ | MRI is test of choice to
evaluate new findings |
| 2) syrinx or hydromyelia of the cord | \ | |
| 3) ↑'d intracranial pressure due to shunt malfunction | / | |
| 4) partial herniation of brain stem & cerebellum | / | |

List some causes of tethered cord } } } "Scar Fixed To Bone"

- Scar from surgery
- Fibroadipose or fibrous filum terminale
- Tumour
- Bony septum

What are some of the other types of occult spinal dysraphisms?

- group of congenital defects that affect formation of spinal column but don't result in an open vertebral canal
- occurs ~1 in 4000 live births
- lipomeningocele
- intradural lipoma
- diastematomyelia
- tight filum terminale
- dermoid cyst/sinus
- aberrant nerve roots
- anterior sacral meningocele
- cauda equina tumour

What are the common lower back features of occult spinal dysraphisms?

- **90% associated with skin abnormality on lower back**
 - skin tag
 - hair tuft
 - subcutaneous lipoma
 - asymmetric gluteal cleft
 - atypical small dimple (off midline, >2.5cm, >0.5cm deep)
 - faun tail
 - human tail
 - dermal vascular malformation
- may also have high arched foot, gait abN'ity, claw toes, etc

What are the common neurologic lesions seen in occult spinal dysraphisms?

- **early Dx } 67% have N neurologic examination during early infancy**
 - if abN, usually UMN lesion } overactivity +/- hyperactive sacral cord reflexes
 - 10% have LMN lesion
- **late Dx } 90% of older kids have abN lower GU tract function**
 - presents w/ absent perineal sensation, back pain, & new onset 2° incontinence
 - UMN lesion, LMN lesion, or combination } usually mixed
 - different lesions produce different findings
 - eg 70% w/ lipoma of cauda equina have UMN lesion
 - 10-20% will progress despite surgery } best results if surgery done early
 - 60% of infants become N after Sx
 - 30% of older kids become N,

Why does occult spinal dysraphism often present with new neurologic findings?

- 1) **compression** on cauda equina or sacral nerve roots by expanding lipoma or lipomeningocele
- 2) **tethered cord** secondary to differential growth rates in bony vertebrae & neural elements
 - while the lower end of cord is held in place by lipoma or thickened filum terminale
 - normally, conus ends at L2 and migrates up to T12 by adulthood
- 3) **fixation of split lumbosacral cord by intravertebral bony spicule or fibrous band**

What is the work-up for suspected occult spinal dysraphisms?

- Hx } pregnancy, meds, perinatal history, milestones, PMHx
 - } urinary signs & symptoms, neurologic signs & symptoms
- P/E } neuro + lower back exam
- investigations } UDS + EMG
- imaging } MRI spine
 - } U/S spine if <3 months of age (vertebral bones have not ossified)

What is the surgical management of occult spinal dysraphisms?

- early surgical Rx recommended } can reverse progression & protect against new lesions
- laminectomy + removal or repair of abN'ity } be careful of nerve roots & cord
- cosmetic surgery for lower back abN'ities

What is sacral agenesis?

- **the absence of part or all of ≥2 lower vertebral bodies } 75% have neurological deficits**
- association with maternal DM
- familial cases assoc'd w/ Currarino syndrome } associated w/ deletions of chromosome 7
 - presacral mass + sacral agenesis + anorectal malformation

How does sacral agenesis usually present?

- bimodal presentation } >75% prenatally or during infancy
 - } ~25% between 4-5yrs of age (often due to failed toilet training)
- N sensation + N lower extremity function
- commonly see flattened buttocks + low, short gluteal cleft
- **UTIs common (~75%)**
- **VUR found in ~40% } more common with UMN lesion**

How do you make the Dx of sacral agenesis?

- AP xray } lateral film if bowel gas obscures sacral area
 } absent vertebral bodies
- MRI } sharp cut off of conus at T12

What are the GU tract findings of sacral agenesis?

→ injury is stable and rarely shows signs of progressive denervation

1) UMN lesion (35%)

- P/E } presence of bulbocavernosus reflex
- UDS } detrusor overactivity
 } exaggerated sacral reflexes
 } absence of voluntary control over sphincter function
 } DSD
 } no EMG denervation of sphincter
- VCUG } thick-walled or trabeculated bladder
 } closed BN

2) LMN lesion (40%)

- P/E } NO bulbocavernosus reflex
- UDS } acontractile bladder
 } diminished or absent sacral reflexes
 } partial or complete denervation of EUS
- VCUG } small, smooth bladder
 } open BN

3) no sign of denervation (25%)

What is the management of sacral agenesis?

→ imaging work-up

- UDS } 75% have neurologic deficit
- renal U/S
- VCUG

→ GU management depends on specific type of neurologic dysfunction

- UMN lesion } anticholinergics
 } augmentation cystoplasty
- LMN lesion } CIC +/- α -agonists
 } BN bulking injections or AUS

→ management of bowel function

- anorectal manometry } can identify abnormalities of internal anal sphincter

What is an imperforate anus?

- 1 in 5000 live births } partial or complete
- occurs **alone or as part of VACTERL syndrome**
→ vertebral, anal, cardiac, tracheo-esophageal fistula, renal, limb
- 1.5x more common in M
→ males have higher lesions
→ females have lower lesions
- imperforate anus may be part of a spectrum of hindgut abN'ities that include sacral agenesis
→ Currarino syndrome } anorectal malformation + sacral agenesis + presacral mass
- 35% high lesion, 15% intermediate lesion, **47% low lesion**, 1% cloacal lesion
→ **level is relative to levator ani muscle**

What is the Wingspread classification of anorectal malformations (CHART)?

	Female	Male
High	- anorectal agenesis +/- rectovaginal fistula	- anorectal agenesis +/- rectourethral (prostatic) fistula
	- rectal atresia	- rectal atresia
Intermediate	- rectovestibular fistula - rectovaginal fistula - anal agenesis without fistula	- rectovestibular urethral fistula - anal agenesis without fistula
Low	- anovestibular fistula - anocutaneous fistula - anal stenosis	- anocutaneous fistula - anal stenosis
cloacal malformation		

What are some of the associated findings of anorectal malformations?

→ **all are more common with higher lesions**

- 1) **fistula with GU tract** (very common, especially if high lesion)
- 2) **GU tract anomalies** } found in 25-50%
 } more common in M
 } **renal agenesis (usually L) and VUR most common**
 } hypospadias
- 3) spinal bony anomalies } occurs in 30-40%
- 4) spinal cord anomalies } found in 20-50%
 } tethered cord, thickened/fatty filum terminale, lipoma of cord most common
- 5) **neurogenic bladder** } often presents as incontinence
 } rare if no spinal cord malformation
 } can be iatrogenic after pull-through surgery
 → pelvic nerve injury less common w/ posterior Pena approach

What is the GU work-up of anorectal malformations?

- 1) P/E } look for fistulous tract from bowel
 } upper & lower extremity exam
 } assessment of bony spine & spinal cord
 → **if evidence of rectal/GU tract fistula, divided colostomy needed before GU tract evaluation**
- 2) imaging } spine MRI (can do U/S if <3months of age as spines haven't fused)
 } renal U/S
 } VCUG
 } UDS + sphincter EMG } reserved for those with abN spine or abN U/S or VCUG
 } performed before & after pull-through operation
 } also if any changes in urinary or fecal continence
- 3) UDS } **UMN lesion most common** (detrusor overactivity +/- DSD)
 } can also have LMN lesion (acontractile bladder, denervated sphincter)

Central Nervous System Insults

What is Cerebral Palsy?

→ **non-progressive brain injury that occurs in perinatal period**

- results in neuromuscular disability or a specific symptom complex or cerebral dysfunction
- 1.5 per 1000 births
- perinatal infection or period of anoxia/hypoxia that affects CNS

What are the RFs for CP?

- prematurity
- maternal UTIs
- LBW (<2kg at birth)
- traumatic birth
- cyanosis at birth
- respiratory distress/arrest/apnea
- mechanic ventilation postnatally
- congenital hydrocephalus
- intraventricular hemorrhage
- neonatal seizures

How does CP usually present?

→ may not present in immediate post-natal period

- delayed gross motor development
- abN stress gait
- abN fine motor performance
- exaggerated deep tendons reflexes
- altered muscle tone
- may have mental retardation

How are the dysfunctions classified?

→ extremities involved } monoplegia, hemiplegia, diplegia, quadraplegia

→ type of neuro dysfunction } spastic, hypotonic, dystonic, athetotic, or some combination

- **spastic diplegia is most common type (67%)**

What are the GU findings of CP?

- **most develop total urinary control** } usually delayed though
- incontinence persists in ~25%
 - incontinence may be functional (physical impairment, mental retardation)
- **abN bladder & urethral sphincter function found in almost all w/ persistent incontinence**
 - 85% have UMN lesion
 - partial UMN lesion is most common UDS finding
 - **overactive detrusor + exaggerated sacral reflexes +/- DSD (25%)**
 - voluntary control over voiding present at capacity
 - LMN lesion more common if hx of cyanosis at birth
- upper tract imaging usually N

What is the management of cerebral palsy & associated GU abN'ities?

- 1) abolish overactive detrusor } anticholinergics
 - } dorsal rhizotomy (if failed conservative management)
 - improves bladder capacity, reduces overactivity, and increases bladder compliance
 - risk of neurologic deterioration is low (<5%)
- 2) ensure complete emptying } CIC may be required if high PVRs
- 3) imaging } only recommended if UTIs

What are the causes of traumatic spinal injuries in kids?

- uncommon in kids
- infants } MVA (70%)
- toddlers } fall from height (50%)
- adolescents } sports-related (30%)

How do SCIs differ in kids?

- mechanism of injury
- differences in spinal cord anatomy
 - horizontal orientation of facet joints in vertebral bodies predisposes to AP subluxation
 - heavy head
 - weaker supportive paraspinal musculature and ligaments
- can often get **SCI without radiologic abnormalities** } SCIWORA
 - from momentary subluxation of bony spine due to elastic ligaments
 - **SCIWORA accounts for ~40% of SCIs in kids**
 - usually see spinal cord edema below level of lesion
 - often a transient phenomenon
 - sensation and motor function often restored quickly
 - bladder and bowel dysfunction may persist considerably longer

What are the GU features associated with traumatic SCI?

- 1) spinal shock phase
 - acontractile bladder
 - nonreactive sphincter
- 2) permanent SCI phase
 - thoracic lesions
 - detrusor overactivity
 - DSD
 - high voiding pressures
 - eventual VUR and hydronephrosis
 - WATCH FOR AUTONOMIC DYSREFLEXIA if level is **higher than T6**
 - sacral lesions (cauda equina)
 - acontractile bladder
 - denervated sphincter
 - incontinence

What is the management of the GU tract in traumatic SCIs?

- initial phase AUR } indwelling foley until stable, then start CIC
- if no voiding after 4-6 weeks, consider UDS
- once voiding starts use CIC as way to assess PVR
- if voiding pressures are high ($>30-40\text{mm H}_2\text{O}$) then must continue CIC
 - can add anticholinergics
 - sphincterotomy can also be used to ensure low pressure voiding
 - botulinum toxin A to sphincter is another option
 - continent catheterizable stoma another option

What is involved in the long-term management of the GU tract in traumatic SCIs?

- UDS to r/o patients at high risk of upper tract deterioration
 - upper spinal cord injuries produce UMN lesion } high risk of upper tract deterioration
 - } overactivity and DSD
 - most sacral cord injuries result in LMN lesion } low pressure bladder emptying
 - } low risk of upper tract deterioration
- U/S to assess upper tracts
- VCUG if recurrent UTIs or signs of BOO on UDS
- surveillance KUB U/S to r/o stones

OTHER

Diseases assoc'd w/ areflexia.

➔ **“SID MD”**

- **Sacral SCI**
- **Iatrogenic (post-op)**
- **DM**
- **Myelodysplasia**
- **DDD**

Diseases assoc'd w/ poor compliance.

→ “SIMM”

- **Sacral SCI**
- **Iatrogenic**
- **Myelodysplasia**
- **MSA**

Diseases assoc'd w/ DESD.

→ “SMCS - T”

- **Suprasacral SCI**
- **MS**
- **Cerebral palsy**
- **Spina bifida**
- **Transverse myelitis**

What are the indications for CIC in kids with neurogenic bladder?

- spinal shock
- hostile UDS features not responding to anti-cholinergics
- upper tract deterioration
- high PVRs
- recurrent UTIs
- incontinence
- high grade VUR

Classify pediatric voiding dysfunction

→ based on impact on upper tracts

Minor disorders (5)	Extraordinary daytime frequency syndrome
	Giggle incontinence
	Stress incontinence
	Postvoid dribbling
	Nocturnal enuresis
Moderate disorders (3)	Lazy bladder syndrome
	Overactive bladder
	Dysfunctional elimination syndromes
Major disorders (4)	Hinman syndrome
	Ochoa syndrome
	Transient UDS dysfunction of infancy
	Myogenic detrusor failure

What is the management of extraordinary daytime frequency syndrome?

- [illegible]

Rx → reinsurance

- reassure family that child is not doing it on purpose

Chapter #124 – Urinary Tract Reconstruction in Kids

THE “FUNCTIONAL” URINARY TRACT

EVALUATION OF THE PATIENT

List the important factors to consider in the evaluation of a child prior to urinary tract reconstruction.

- commitment of patient & family is essential
- renal function
- upper tract imaging } r/o obstruction and VUR
- UDS } bladder capacity & compliance
 - } BN & EUS function and synergy
- bladder emptying
- potential for CIC } native urethral quality, family support, patient skill and willingness

PREPARATION OF THE PATIENT

List the important factors to consider in preparing the patient for urinary tract reconstruction.

- sterile urine
- bowel cleansing
- optimization of general health of patient } nutritional status, co-morbidities, etc

ANTI-REFLUX

What are the different open surgical techniques used in the management of VUR?

- pre-op cystoscopy
- Pfannenstiel incision made 2cm above symphysis pubis
- a) intravesical**
 - Politano-Leadbetter (suprahiatal tunnel)
 - Glenn-Anderson (infrahiatal tunnel)
 - Cohen Cross-trigonal } **most commonly used intra-vesical reimplantation**
- b) extravesical**
 - Lich-Gregoire
- c) combined**
 - Paquin technique } extravesical approach to ureter + Politano-Leadbetter intravesical

What are the issues with ureteral reimplantation into bowel segments?

- 1) Colonic
- 2) Ileal } most challenging to make anti-reflux mechanism with ileum
- 3) stomach

Describe the different types of uretero-COLONIC anastomoses?

→ NON-REFLUXING

- 1) Leadbetter-Clarke } extra-colonic
→ **HIGH stricture rate (14%)**
- 2) Strickler } extra-colonic
→ **HIGH stricture rate (14%)**
- 3) Pagano } extra-colonic
} anterior version of GOODWIN
→ **LOW COMPLICATION rate**
→ **LOWEST stricture rate (6%)**
- 4) Goodwin } trans-colonic
} posterior version of PAGANO
} colonic version of LE DUC ureteroenteric anastomosis
→ **limited data**

→ REFLUXING

- 1) Cordonnier & Nesbit } direct refluxing anastomosis
} not preferred for ureterosigmoidostomies
} colonic version of BRICKER ureteroenteric anastomosis

Describe the different types of uretero-ENTERIC anastomoses? } “BW SLUT HAMMOCK”

1) REFLUXING

- a) Bricker } end-to-side (aka Leadbetter)
} full-thickness ureter to full-thickness small bowel anastomosis
→ **simple with LOW COMPLICATION rate**
→ **LOW stricture rate (6%)**
- b) Wallace } end-to-end
} 3 different configurations used
→ **contraindicated if extensive CIS or high likelihood of recurrence in one ureter**
→ **LOWEST COMPLICATION RATE of any ureterointestinal anastomosis**
(stricture rate 3%, leak rate 2%)

2) NON-REFLUXING

- a) Griffiths Split-nipple
- b) Le Duc } transenteric
→ **LOWEST stricture rate with modification (3% vs previous 15%)**
→ **HIGHEST success rate for anti-reflux**
- c) Ureteral compression by seromuscular layer (“Ghoneim”)
→ **LOW reflux rate (3%)**
- d) Tunneled anastomosis
→ **not used often so limited data**
- e) Hammock } ureters joined Wallace-style then implanted in nonrefluxing manner
→ **HIGH reflux rate (20%)**

Describe the different types of intestinal anti-reflux valves?

- ureters anastomosed using Bricker or Wallace
- end of bowel distal to anastomosis is used to create one-way valve
- **failure of valve or stenosis of anastomosis affects both kidneys**
- 1) intussuscepted ileocecal valve
→ **HIGH FAILURE RATE (nipple reduces)**
- 2) intussuscepted ileal nipple valve
→ **10% COMPLICATION RATE** (5% stones, 4% stenosis, and 1% prolapse)
- 3) ileal nipple valve placed into colon
→ **SIMPLEST TYPE**

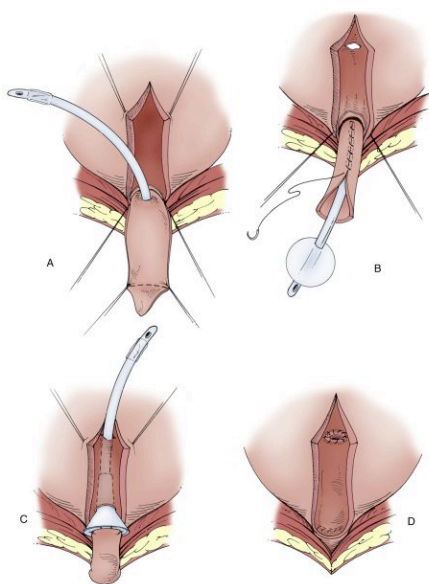
BLADDER NECK RECONSTRUCTION

List the different techniques to achieve urinary continence through BN and EUS reconstruction.

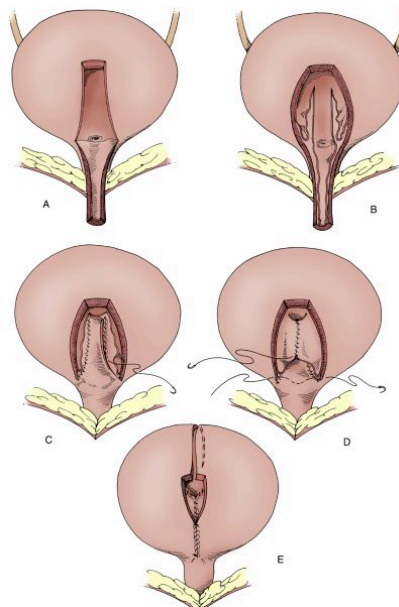
- 1) BN reconstruction } eg Young-Dees-Leadbetter repair
eg Pippi-Salle procedure
eg Kropp anterior detrusor tube
- 2) Fascial Sling } better if done with augmentation cystoplasty (for neurogenic bladders)
- 3) BN bulking agents } no good long-term success
- 4) AUS } mechanical issues but can give high rate of continence

KEY POINTS: BLADDER NECK RECONSTRUCTION

- Any bladder neck repair other than placement of an artificial urinary sphincter, particularly in combination with augmentation cystoplasty, is likely to make spontaneous voiding inadequate.
- Young-Dees-Leadbetter bladder neck repair in the spina bifida population may have variable success related to the underlying neurogenic dysfunction.
- Fascial slings have been used more extensively and with better results in girls than in boys with neurogenic sphincter incompetence, although those results have varied greatly.
- Experience does not yet suggest that injection of bladder neck bulking agents has a lasting effect on severe neurogenic sphincter incompetence.
- A functioning, well-positioned artificial urinary sphincter device generally provides good outflow resistance and is best suited for patients who can empty adequately with spontaneous voiding.
- Urethral lengthening procedures construct an effective flap valve mechanism for continence that disrupts any chance of spontaneous voiding and may make catheterization per urethra difficult.
- The success of all bladder neck repairs in the neurogenic population is improved when the repair is associated with bladder augmentation.
- Any bladder neck repair may unmask or result in new bladder hostility; careful follow-up is mandatory.



→ BN RECONSTRUCTION } KROPP



→ BN RECONSTRUCTION } PIPPI-SALLE

AUGMENTATION CYSTOPLASTY

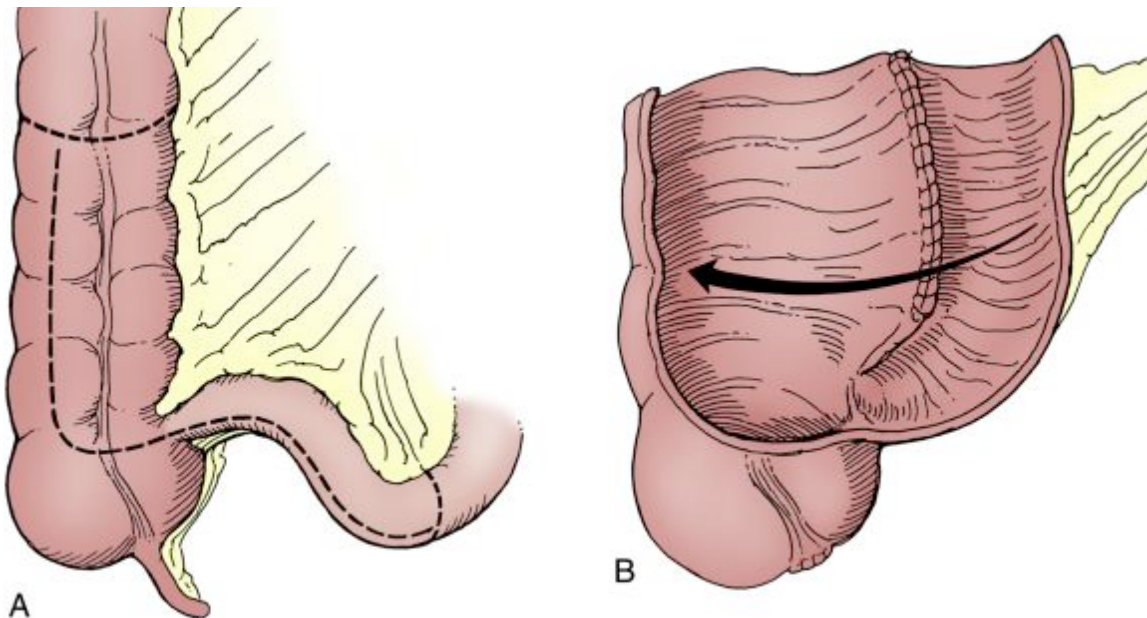
What are the key management steps in performing an augmentation cystoplasty?

- pre-op cysto to r/o abN anatomy that may affect surgery } leave bladder full if planning ureteric reimplantation
- midline incision preferred
- widely open native bladder to prevent narrow-mouthed anastomosis } sagittally bivalved
 - OLD SCHOOL } supratrigonal cystectomy
- bowel segment detubularized along anti-mesenteric border & reconfigured into spherical shape
 - maximize volume
 - blunting of bowel contractions
 - improvement of overall capacity & compliance

\ } colonic segments generate more
/ } pressure than ileal segments
despite detubularization
- consider cutaneous catheterizable stoma if unable to perform CIC per urethra or if sensate urethra
- S/P tube placed +/- urethral catheter
- JP drain placed

What are the different options for augmentation cystoplasty?

- consider cutaneous catheterizable stoma if unable to perform CIC per urethra or if sensate urethra
- 1) Ileocystoplasty } 20-40cm segment
- 2) Ileocecocolocystoplasty } like modified-Indiana
 - appendix can be used as catheterizable conduit
 - removal of ileocecal valve can cause serious diarrhea in some kids
- 3) Sigmoid cystoplasty
- 4) Gastrocystoplasty } use of antrum VS use of body
 - mobilized on gastroepiploic artery
- 5) ureterocystoplasty
- 6) autoaugmentation ("neo-diverticulum") } improves compliance BUT limited increase in capacity
- 7) seromuscular enterocystoplasty (coverage of urothelium bulge with bowel)



→ ILEOCECOCYSTOPLASTY } modified-Indiana pouch style

KEY POINTS: AUGMENTATION CYSTOPLASTY

- No matter the gastrointestinal segment used, that segment should be reconfigured and widely anastomosed to the native bladder to maximize capacity and compliance.
- Failures to achieve adequate compliance are rare (~5%) and are usually related to rhythmic pressure contractions.
- Gastrointestinal effects are rare, although chronic diarrhea may occur if the ileocecal segment is used in the neurogenic population.
- Ammonium resorption from urine in contact with intestinal mucosa can cause chronic metabolic acidosis, particularly among patients with renal insufficiency.
- Acid secretion after gastrocystoplasty results in two unique potential complications: hematuria-dysuria syndrome and acute metabolic alkalosis.
- Bacteriuria is common after cystoplasty and does not always require treatment.
- Bladder calculi, usually struvite, occur in 10% to 30% of patients after augmentation cystoplasty but may be minimized by routine irrigations for mucus.
- Adenocarcinoma in the intestinal segment has been reported as early as 4 years after augmentation cystoplasty but, thus far, has not occurred with the frequency noted after ureterosigmoidostomy.
- Delayed spontaneous perforation of the bowel segment can be expected in 5% of patients after augmentation. It has occurred most frequently in colonic segments used in the neurogenic population.
- Ureterocystoplasty avoids the complications associated with bowel segments but may not provide adequate volume if the ureter is not remarkably dilated.
- Autoaugmentation, no matter what the technique, seldom adds significant capacity and may not always improve compliance long term.
- More experience and longer follow-up with seromuscular enterocystoplasty are needed to determine its appropriate role.
- Care for the underlying bladder dysfunction should be improved to lower the need for augmentation cystoplasty.

What are the advantages & disadvantages of the different intestinal segments?

	ADVANTAGES	DISADVANTAGES
STOMACH	<ul style="list-style-type: none"> - less permeable to urinary solutes - has net excretion of H⁺ and CL⁻ - produces less mucus - acidic urine produces less stomal skin irritation - rarely have lyte abN'ities if renal function is normal - lower incidence of bacteriuria - avoids adhesions which are more common in lower abdomen 	<ul style="list-style-type: none"> - can occasionally get severe hypoCL hypoK MET ALKALOSIS - 10% incidence of obstruction - elevated gastrin levels a risk for major intestinal ulcers - decreases stomach volume - high complications of gastric reconstruction (Billroth I) - hematuria-dysuria syndrome
JEJUNUM		<ul style="list-style-type: none"> - severe electrolyte abN'ities such as hypoNa hypoCL hyperK MET ACIDOSIS - Fe deficiency - Ca deficiency
ILEUM	<ul style="list-style-type: none"> - mobile - small diameter - constant blood supply 	<ul style="list-style-type: none"> - can result in anemia (Vit B12 def) - diarrhea (lack of bile salt reabsorption) - fat malabsorption (Vit A, D, E, K) - sometimes has excessive mesentery or very short mesentery - obstruction (10%) more common cf colon - hyperCl hypoK MET ACIDOSIS
COLON	<ul style="list-style-type: none"> - easily mobilized - upper colon safe to use even after pelvic radiation - fewer nutritional problems - lower incidence of bowel obstruction (4%) - easier to make anti-reflux anastomosis via submucosal tunnel 	<ul style="list-style-type: none"> - if ileocecal valve used can result in diarrhea, bacterial colonization of ileum resulting in abN absorption and fluid loss - hyperCl hypoK MET ACIDOSIS (hypoK is more common with colon cf ileum)

What are the potential METABOLIC COMPLICATIONS of urinary intestinal diversion?

→ mnemonic is "G-DIVERIONS"

- 1) **G**rowth retardation } bone growth & bone healing affected
 } long term diversions place patient at higher risk of fractures & complications after orthopedic surgery
- 2) **D**rug metabolism abN'ities } for drugs absorbed by GI tract & excreted unchanged renally
 } eg Dilantin, chemo (MTX), certain ABx (nitrofurantoin)
 Rx → alkalization + drainage during chemo
- 3) **I**nfections (persistent, recurrent) } increased incidence of bacteriuria, bacteremia, sepsis
 } more common after cololecystoplasty cf ileocystoplasty
 } renal deterioration more common with pure *Proteus* or *Pseudomonas* bacteriuria
 → may warrant Rx even if asymptomatic
- 4) **V**itamin B12 deficiency } mainly from use of distal ileum (worst with Kock pouch – 80cm)
- 5) **E**lectrolyte abnormalities } depends on segment of bowel used
 } stomach → hypoCl, hypoK metabolic alkalosis
 } jejunum → hypoNa, hypoCl, hyperK metabolic acidosis
 } ileum and colon → hyperCl metabolic acidosis
- 6) **R**enal failure
- 7) **S**tones } most stones are **Ca/Mg/NH₄/PO₄**
 } more common w/ hyperCl met acidosis, pre-existing pyelo, & urease +ve UTI's
 } more common with ileal conduits (~10%) cf colon conduits (~4%)
- 8) **I**ntestinal problems (see below) } malabsorption, diarrhea, etc
- 9) **O**steomalacia } **due to acidosis that reduces mineralized bone (release of Ca), renal Vit D resistance, or excessive Ca loss by kidneys**
 } most common with ureterosigmoidostomies
 } lethargy, joint pain (esp wt-bearing), proximal myopathy
 Rx → correct acidosis, Ca +/- 1 α -hydroxycholecalciferol supplements
- 10) **N**eoplasms } adenoCa, adenomatous polyps, sarcomas, TCC
 } usually don't manifest for 10-20yrs
 } **adenocarcinoma most common** and may develop from urothelium or bowel
 } most common when urothelium + colonic epithelium & both bathed by feces
 Rx → routine C-scopes for ureterosigmoidostomies
 → annual surveillance of any diversion after ~3yrs
 → always remove ureterointestinal anastomoses after defunctionalized
- 11) **S**ensorium alterations } from **Mg deficiency, drug intoxication, or abN NH₄ metabolism**
 → most likely NH₄ related (esp in cirrhotics)
 } can result in ammoniagenic coma
 } most common in ureterosigmoidostomies
 Rx → rectal tube/foley + neomycin + low protein + lactulose
 → arginine glutamate (50g in 1L D5W) if severe

CONTINENT URINARY DIVERSIONS

- for kids WITHOUT neurologic deficits, normal sensation in the native urethra can prevent compliance with a routine CIC schedule due to pain/discomfort
- consider CONTINENT CATHETERIZABLE STOMA in these kids

CONTINENCE MECHANISMS AND CATHETERIZABLE SEGMENTS

Describe the important principles of a Mitrofanoff procedure.

- mobilize ascending colon & cecum to allow adequate mobilization of appendix & mesentery
- harvest small cuff of cecum with appendix } used to decrease stomal stenosis risk
- location to implant into bladder is chosen based on:
 - length of appendix \
 - mobility of bladder } appendix usually tunneled into POSTEROLATERAL
 - location of stoma / position within bladder
- appendix brought to skin in tension-free manner
- ensure easy catheterizability after each step of surgery

What is the most common complication of a Mitrofanoff procedure

→ stomal stenosis } 10-20%

What are alternatives to the appendix for a Mitrofanoff procedure?

→ to prevent problems with catheterization, maintain as short a conduit as possible

- 1) ureter } stomal stenosis even more common
- 2) fallopian tube } stomal stenosis problems
- 3) gastric tube
- 4) Yang-Monti tapered ileal segment } excellent results
- 5) ileocecal valve
- 6) continent vesicostomy } bladder tube placed through rectus muscle

ANTEGRADE CONTINENCE ENEMAS

URINARY UNDIVERSION

Chapter #125 – Hypospadias

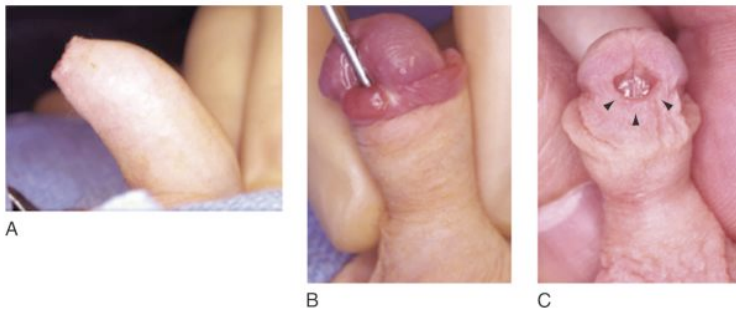
DEFINITION, DIAGNOSIS, AND CLASSIFICATION

What is hypospadias?

- an association of 3 anomalies of the penis
 - 1) abN ventral opening of urethral meatus (anywhere from ventral aspect of glans to perineum)
 - 2) abN ventral chordee
 - presence is variable (~25%)
 - 3) abN distribution of foreskin with a dorsal “hood” and deficient ventral foreskin
 - presence is variable

How is hypospadias diagnosed?

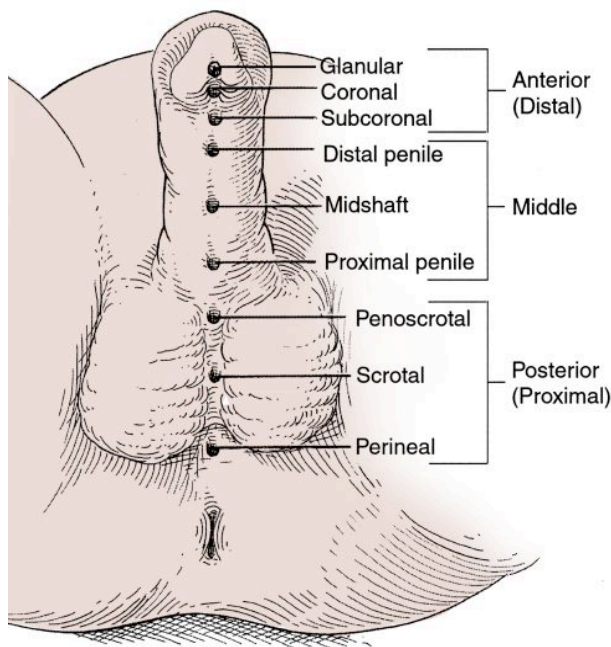
- most found at newborn P/E
 - may be missed in certain boys
 - a) milder forms of hypospadias
 - b) non-retractile prepuce
 - c) megameatus intact prepuce variant (MIP) } likely distal invagination problem
- **isolated hypospadias may be only visible indication of a significant underlying abN’ity**



- MIP VARIANT } A – NORMAL FORESKIN
 B – GAPING HYPOSPADIAIC MEATUS
 C – TYPICAL APPEARANCE OF MEATUS AFTER NEWBORN Cx

What is the classification of hypospadias?

- many different classifications have been proposed
 → **based on location of hypospadiac meatus AFTER REPAIR of chordee (orthoplasty)**
- 1) anterior (distal) → 50-70%
 - a) glanular
 - b) coronal
 - c) subcoronal
 - 2) middle → ~30%
 - a) distal penile
 - b) midshaft
 - c) proximal penile
 - 3) posterior (proximal) → ~20%
 - a) penoscrotal
 - b) scrotal
 - c) perineal



→ CLASSIFICATION OF HYPOSPADIAS (AFTER ORTHOPLASTY)

DEVELOPMENT

Describe the embryologic development of the urethral plate & urethra.

- origin of urethral plate is an outgrowth from the walls of the cloaca and urogenital sinus
- 4th week } urethral plate seen as a thickening of anterior wall of the endodermal cloaca
- **primary urethral groove established by development of the urethral folds on the ventrum of the phallic portion of the UG sinus on either side of the urethral plate**
 - these folds are covered by surface epithelium
- 8th wk } **secondary urethral groove** after disintegration of the roof of primary groove
 - continuation of this process results in **definitive urethral groove**
- 9th week } preputial tissue exists as dorsal hood at this stage
 - urethral meatus is well back on ventral surface
- 11th wk in males } **↑'d Leydig cell function (more T) results in fusing of urethral folds ventrally in midline to form the urethra**
 - **proximal glanular urethra** develops from urethral plate (**endodermal origin**)
 - **distal glanular urethra** develops from lamellar ingrowth of surface epithelium (grows in toward distal urethral plate) (**ectodermal origin**)
 - “ectodermal ingrowth theory”
- 20th wk } complete preputial covering of the glans develops

What is the “endodermal differentiation theory”?

- opposes the ectodermal ingrowth theory
- states urethral plate extends distally all the way to tip of phallus & maintains patency & continuity throughout urethral development
- states entire urethra originates from UG sinus/endoderm (no ectoderm)
- endodermal tissue can differentiate distally into stratified squamous epithelium under proper signalling

Describe the embryologic development of the neurovascular anatomy of the penis.

→ **similar innervation but different vascularity (particularly distally)**

- nerves } originate proximally as 2 well-defined bundles under pubic rami superior & slightly lateral to the urethra
 - } as 2 crural bodies converge to form corpus cavernosa, the nerves diverge to enter jxn b/w corpora cavernosa & urethral spongiosum
 - } nerves fan out from 11- and 1-o'clock positions all along penis
 - no nerves at 12-o'clock position
- vascularity } extensive vascularity of distal urethral spongiosum & glans in hypospadiac penises cf normal penises
 - incision into these rich endothelial-lined sinuses may result in release of EGFs that encourage tissue repair w/o significant scar/stricture

ETIOLOGY

What is the etiology of hypospadias?

→ **multi-factorial etiology**

a) **environmental or endocrine disruptors**

- earlier maternal progestin use associated with more proximal hypospadias
- hypospadias more common in M conceived by IVF (early progesterone for pregnancy support)

b) **endocrinopathy, enzymatic abN'ity or local tissue abN'ity**

- abN androgen production by fetal testis
- partial AIS in target tissues of developing external genitalia (Reifenstein's)
- insufficient T and/or DHT synthesis (defective/deficient 5AR enzyme)
- defective androgen receptor quality and/or quantity
- 3 β -hydroxysteroid dehydrogenase deficiency (produces profound CAH) associated incomplete masculine development & hypospadias

c) **manifestation of arrested development (most plausible)**

- premature cessation of T/DHT stimulation 2° to premature involution of fetal Leydig cells

Why does the "arrested development" theory of hypospadias make sense?

- when meatus is still proximally located, dorsal hood exists and penis is curved
- penile curvature is part of early stages of N penile development
- dorsal hood is present early in N penile development

What are the 3 main theories to explain the cause of congenital chordee WITH hypospadias?

- 1) abN development of urethral plate } Snodgrass disagrees
- 2) abN fibrotic mesenchymal tissue at the urethral meatus
- 3) corporal disproportion } differential growth of N dorsal cavernosal tissue & abN ventral tissue

What are the 4 main theories to explain the cause of congenital chordee WITHOUT hypospadias?

- 1) skin tethering
- 2) fibrotic Dartos & Buck's fascia
- 3) corporal disproportion
- 4) congenitally short urethra (rare)

What are the 4 classes of congenital chordee WITHOUT hypospadias?

→ Devine and Horton '73

- type I } very thin "mucous membrane" urethra + **deficiency of corpus spongiosum** from site of curvature out to glans (most severe defect)
- type II } urethra surrounded by N corpus spongiosum but with **abN Buck's & dartos fascia**
- type III } **abN dartos fascia only**
- type IV } **corporal disproportion**
- type V } congenitally short urethra (rare)

EPIDEMIOLOGY

How common is hypospadias?

- approximately **1 in 250 live male births**
- majority are distal hypospadias
- according to MACDP and BDMP, rate of hypospadias is increasing
 - not just due to increased reporting of minor forms } would then expect ratio of mild to severe forms to increase
 - proportionally more severe cases of hypospadias are being reported
- familial prevalence exists
 - 6-8% of fathers of affected boys also have hypospadias
 - 14% of male siblings of affected boys have hypospadias
- 8.5x more common in one of monozygotic male twins compared w/ singleton live male births
 - may be due to inability of single placenta and lower hCG levels to meet requirements of 2 developing male fetuses

ASSOCIATED FINDINGS

How common are chromosomal abnormalities in boys with hypospadias?

- ~6% of boys with hypospadias } majority found in cases of severe posterior hypospadias
- ~5% of boys with UDT
- ~22% of boys with hypospadias + UDT
 - **must r/o intersex state in these boys even if not ambiguous genitalia**
 - **~30% of boys w/ hypospadias + UDT + NON-ambiguous genitalia are intersex**
 - **intersex 3x more common if cryptorchid testis is nonpalpable**
(50% nonpalpable vs 15% palpable)
 - **intersex more common with proximal hypospadias**

List some anomalies associated with hypospadias?

- 1) **UDT** (7-9%) } mainly in boys with posterior hypospadias
 - 2) **inguinal hernia/hydrocele** (10-15%) } no correlation to location of meatus
 - 3) **49 different syndromes** in which hypospadias is an associated finding
 - eg WAGR, Fraser's, Beckwith-Wiedemann, Simpson-Golabi-Behmel, Schinzel-Giedion (100%)
 - ~80% also associated with micropenis, scrotal abN'ity, and UDT
 - supports endocrinopathic cause of hypospadias
- **NO NEED TO ASSESS UPPER TRACTS } NOT ASSOCIATED WITH RENAL ANOMALIES**

SPECIAL CONSIDERATIONS: PRE-OP

What are the indications for hypospadias repair?

- 1) to allow micturition in standing position
 - 2) to allow sexual intercourse
 - 3) to allow effective insemination
 - 4) cosmesis
- most males with distal hypospadias have no medical indications for repair other than cosmesis

What is involved in the evaluation of the child w/ hypospadias?

→ Hx

- difficulty w/ voiding
- degree of curvature
- UTIs
- Antenatal hx + medication exposure (eg progestins)
- Developmental hx } milestones
- PMHx, meds
- FHx hypospadias

→ P/E

- Growth chart plot
- Abdo exam } masses, SP/flank tenderness, full bladder
- external genitalia } micropenis, meatal location, deficiency of spongiosum, hernia, hydrocele,

and UDT

→ Intersex evaluation if necessary

- for those w/ posterior hypospadias and/or associated UDT
- “rule of 3” } investigate if 2/3 is abN (R testis, L testis, hypospadias)

→ Imaging

- **no routine imaging if isolated hypospadias**, esp if middle or anterior in location
- more important in pts w/ posterior hypospadias } VCUG

→ pre-op hormonal manipulation

- controversial } stimulation (hCG) vs supplementation (T, DHT) vs nothing
- increases penile size & length (~50%), allowing for more simple repairs

What are the indications to evaluate for an endocrine abnormality and/or an intersex state?

- 1) hypospadias + UDT
- 2) isolated posterior hypospadias

What tests are involved in the evaluation of a child with hypospadias for endocrine abN’ity or intersex?

- lab tests } karyotype, molecular testing, biochemical testing, gonadal (histology) testing
- abN karyotype found in ~20% with concomitant hypospadias + UDT
- imaging } U/S + genitography (RUG)
- } pre-op VCUG +/- cysto if concomitant scrotal or perineal defect
- to evaluate frequently present, and extent of, prostatic utricle
- “FUUKED Large, Then Gone After 17”

What is the role of pre-op androgen stimulation?

- may decrease degree of hypospadias & chordee, improve tissue quality & allow for more simple repair
- twice weekly s.c. or i.m. hCG (250 or 500 IU depending on age) for 6-8 weeks pre-op
- for kids <5yrs only
- may see increase in penile size & length and a decrease in hypospadias & chordee severity
- may notice increased vascularity & thickness of proximal corpus spongiosum

What is the role of pre-op androgen supplementation/replacement?

- mainly for small penis } usually associated with proximal hypospadias
- testosterone ointment x 2weeks pre-op
- inconsistent results
- q1week i.m. testosterone enanthate (2mg/kg/dose) for 2-3 weeks pre-op
- increase in penile size
- increase in available skin and local vascularity
- daily DHT cream x 4weeks pre-op
- increase in penile length and circumference
- **pre-pubertal exogenous testosterone DOES NOT adversely affect ultimate penile growth**
- supported by studies of men with true precocious puberty or CAH

GENERAL PRINCIPLES OF HYPOSPADIAS REPAIR

What are the 5 basic principles important in hypospadias repair?

- 1) correction of penile curvature (orthoplasty)
- 2) urethroplasty
- 3) meatoplasty
- 4) glanuloplasty
- 5) adequate skin coverage

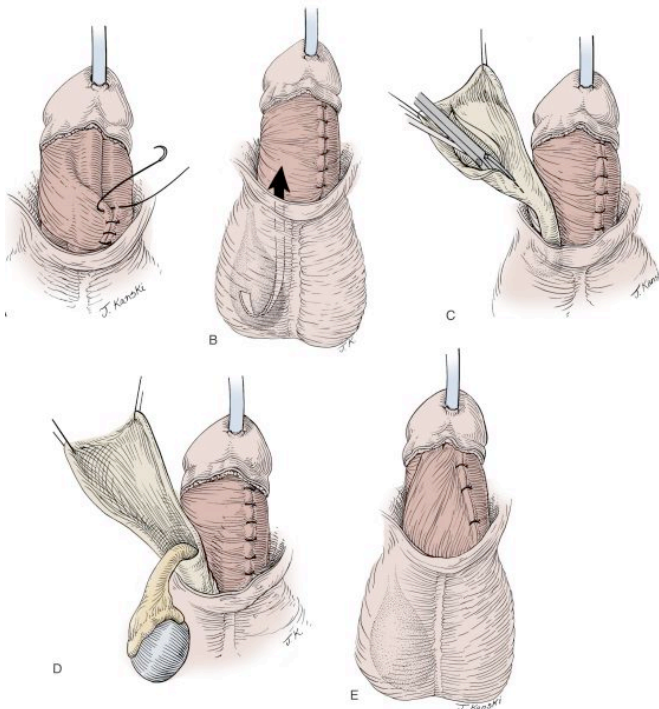
Orthoplasty

What is the importance of assessing penile curvature?

- critical step in hypospadias repair } usually performed after degloving of penile shaft skin
- artificial erection (NS) vs pharmacologic erection (PGE1)
 - physiologic erection testing allows for more accurate & cont'd assessment

What are the management options for chordee with or without hypospadias?

- dictated by degree & direction of curvature as well as penile size
- 1) release of skin tethering +/- skin transfer
 - for mild "cutaneous chordee"
 - may also employ ventrally transposed, pedicled preputial flap
- 2) Nesbit
 - shortens penile length
 - removal of transverse elliptical segments of tunica albuginea from longer side
 - can be used to correct "glans tilt" deformity
 - can be combined with Heineke-Mikulicz
- 3) Heineke-Mikulicz
 - transverse incisions in tunica albuginea on shorter side closed longitudinally to gain length
- 4) tunica albuginea plication ("Baskin & Duckett")
 - shortens penile length
 - degloving of penile shaft skin + mobilization of NVB bilaterally
 - parallel longitudinal incisions made (~1cm long & ~1cm apart) on anterolateral tunica albuginea
 - outer edges of parallel incisions are approximated with 4-0 PDS
- 5) corporal rotation ("Koff & Eakins")
 - ventral midline longitudinal incision + medial rotation of corporal bodies + suture fixation of dorsal aspect of corpora cavernosa +/- incision of corporal septum
 - allows single-stage reconstruction without shortening length
- 6) grafts } dermal graft
 - ideal for short phallus with severe ventral chordee
 - dermal graft harvested from non-hirsute donor site (typically groin)
 - graft taken slightly longer than ventral defect made by transverse linear corporotomy
 - dermal graft anastomosed to edges of corporal defect with running 6-0 vicryl
 - } SIS interposition graft
 - for severe ventral chordee
 - porcine small intestinal submucosa } acellular collagen-based material
 - single-layer SIS better than multi-layer
 - best if used at 1st stage of 2-staged repair of severe hypospadias
 - } tunica vaginalis free graft
 - for severe chordee
 - free graft used as a ventral corporal patch
- 7) Total penile disassembly
 - ideal for correction of a) glans tilt, b) ventral chordee without hypospadias, and c) chordee with hypospadias
 - radical approach involving penile disassembly + corporoplasty



→ HYPOSPADIAS REPAIR } NEOURETHRAL COVERAGE (2ND LAYER)
 } TUNICA VAGINALIS FLAP

Meatoplasty and Glanuloplasty

What are the options for meatal & glanular reconstruction for hypospadias repair?

→ successful completion of meatoplasty is dependent on good glanuloplasty, and vice versa

- 1) V-flap glanuloplasty
 - adjunct to tubularized skin graft urethroplasty
 - extensive dissection of glans w/ development of midline anterior flap of glans epithelium
 - removal of subepithelial tissue from glans flap
 - flap fixed to tunica of corpora cavernosa
 - makes widely patent, complication-free meatus
- 2) double-faced preputial flap
 - flap transposed ventrally for enhancement of glans and meatus
 - for small and deformed glans
- 3) glanular W-flap meatoplasty

Penile Skin Coverage

What are the options for ensuring adequate skin coverage of the penis after hypospadias repair?

- 1) ventral transfer of preputial skin
 - either with a buttonhole through the skin for through-passage of glans penis OR midline longitudinal split of prepuce or dorsal penile skin + lateral transfer of skin
- 2) transverse outer preputial island flap

- bladder spasms } judicious use of anti-cholinergics in catheterized patients

INTRA-OP ALGORITHM

What are the 4 main factors to consider when determining the appropriate repair for hypospadias?

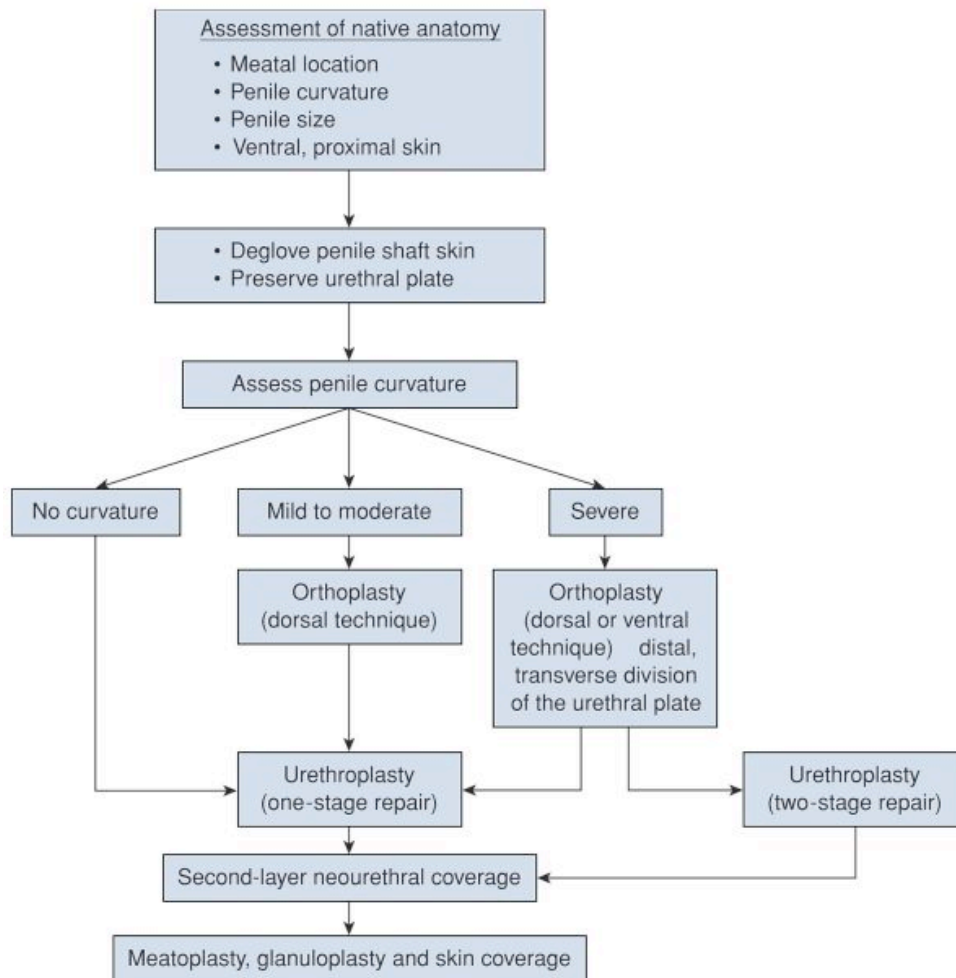
- 1) native meatal location
- 2) penile size
- 3) penile curvature
- 4) characteristics of ventral, proximal shaft skin

What is the recommended approach to hypospadias repair?

- 1) deglove penile shaft skin + preserve urethral plate
→ if very proximal hypospadias, no need to preserve plate
- 2) assess degree of curvature prior to formal repair
 - a) if no chordee } 1-stage urethroplasty
 - b) if mild to moderate chordee } orthoplasty + 1-stage urethroplasty
 - c) if severe chordee } orthoplasty +/- transverse release of tethering urethral plate +
1- or 2-stage urethroplasty
- 3) 2nd layer neourethral coverage
- 4) meatoplasty + glanuloplasty + skin coverage

What are the preferred urethroplasty techniques used for the different types of hypospadias?

- use of well-vascularized local tissue is preferred
- during orthoplasty, when possible, should preserve urethral plate for incorporation into urethroplasty
 - may need to release if severe chordee with plate that is tethering penis
 - usually able to preserve urethral plate for all cases except for very proximal hypospadias
- 1) **distal** } typically repaired with an **advancement technique**
 - } when simple advancement is not sufficient or appropriate, defects may be managed with various **tubularized** or flap techniques
 - a) simple tubularization if deep glanular groove + wide urethral plate
 - eg TIP
 - may need to make midline longitudinal incision of urethral plate if glanular groove is shallow and/or urethral plate is narrow
 - b) various perimeatal-based flap techniques also good if shallow glanular groove + narrow urethral plate
 - not favored due to inferior meatal cosmesis and poor flap vascularity
- 2) **middle** } typically amenable to **tubularization** or vascularized flap techniques
- 3) **proximal** } various **tubularization or flap** techniques or 2-stage techniques
 - } onlay technique may be preferred for a small penis w/ a shallow glanular groove



→ INTRA-OP ALGORITHM FOR HYPOSPADIAS REPAIR

What are the management options for hypospadias?

- Distal } Advancements techniques eg MAGPI
 - } Tubularization techniques eg TIP, Thiersch-Duplay
 - } Flaps eg Mathieu
- Middle } Tubularization techniques eg TIP
 - } Flaps eg Mathieu, Onlay flaps (OIF, split-prepuce OIF)
- Proximal } Single stage urethroplasty
 - Flaps eg OIF, onlay-tube-onlay
 - Tubularization techniques eg Duckett TPIF, Koyangi
 - } 2-Stage urethroplasty

→ main types of repairs } ATF = M, TTD, MO

- Advancement = Magpi
- Tubularized = Thiersch-Duplay, TIP, Duckett
- Flaps = Mathieu, Onlays

What are the different types of techniques used for DISTAL HYPOSPADIAS repair?

➔ ADVANCEMENT TECHNIQUES ***

- excellent fxn'l & cosmetic result } as long as there is adequate urethral mobility & no chordee
-
-
-
- } >95% long term success rates
- } re-operation rate of ~2%

- ## ➔ TUBULARIZATION TECHNIQUES ***

- for **glanular hypospadias**
- excellent functional and cosmetic results } re-operation rate of ~2%

- modification of Thiersch-Duplay for **distal & some middle hypospadias**
- involves longitudinal midline incision of urethral plate, fashioning of wide meatus, and 2nd layer coverage of neourethral with sc dartos flap
- good functional results } >95% success rate
 - } complication rate of 1-5% (for primary repair)
 - low flow rate common after TIP } improves with age

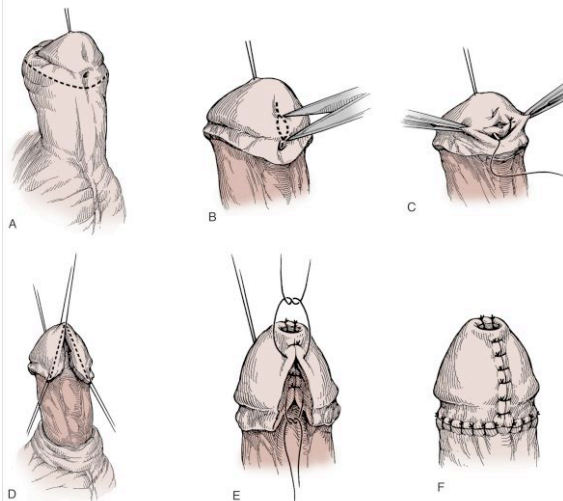
- perimeatal-based flap technique
- for **coronal, subcoronal, & some middle hypospadias**
- requires adequate ventral penile shaft skin
- excellent functional results } complication rate of ~1%
- cosmetic result is variable

- modification of Mathieu flap
 - includes dissection of urethral plate distal to meatus + advancement of approximated (now tubularized) flaps to the tip of the glans
- for **coronal & subcoronal hypospadias**
- requires adequate ventral penile shaft skin
 - often requires complex rotational skin flaps for coverage

- "pyramid" procedure
- MAGPI
- Thiersch-Duplay
- Mathieu flap

Describe the main steps of a MAGPI distal hypospadias repair.

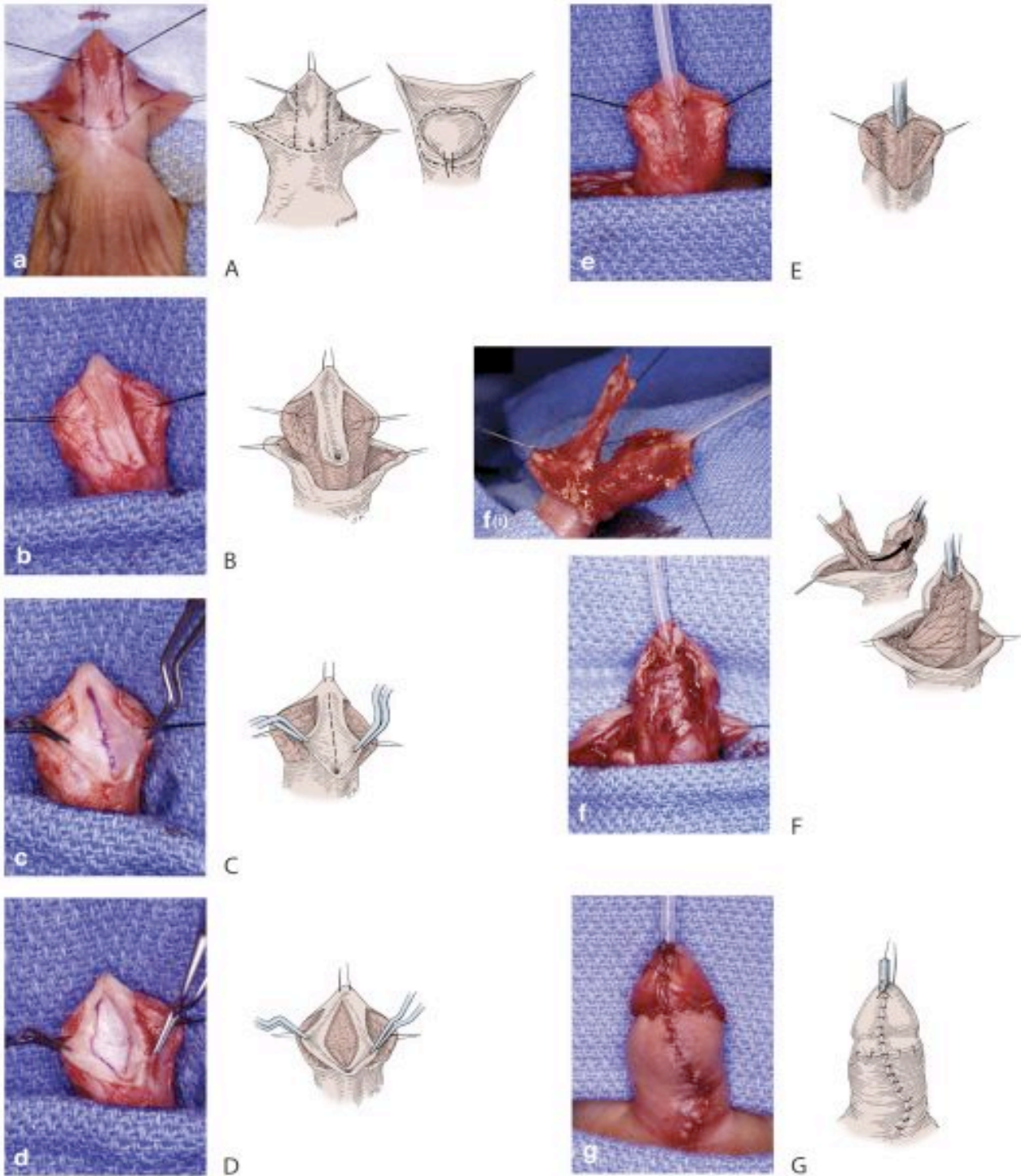
- circumferential subcoronal incision } made 5mm proximal and parallel to corona of glans
- if present, the typical transverse glanular tissue “bridge” in the urethral plate (between hypospadiac meatus and distal glanular groove), is incised longitudinally
- incised glanular tissue bridge are then reapproximated transversely in Heineke-Mikulicz fashion
- ventral edge of meatus is pulled distally (with aid of stay suture) and medial edges of glans are trimmed
- midline approximation of glans edges in 2 layers with simple, interrupted sutures
- superficial approximation of glans and skin with simple, interrupted sutures



→ DISTAL HYPOSPADIAS REPAIR } MAGPI REPAIR

Describe the main steps of a TIP urethroplasty for distal hypospadias.

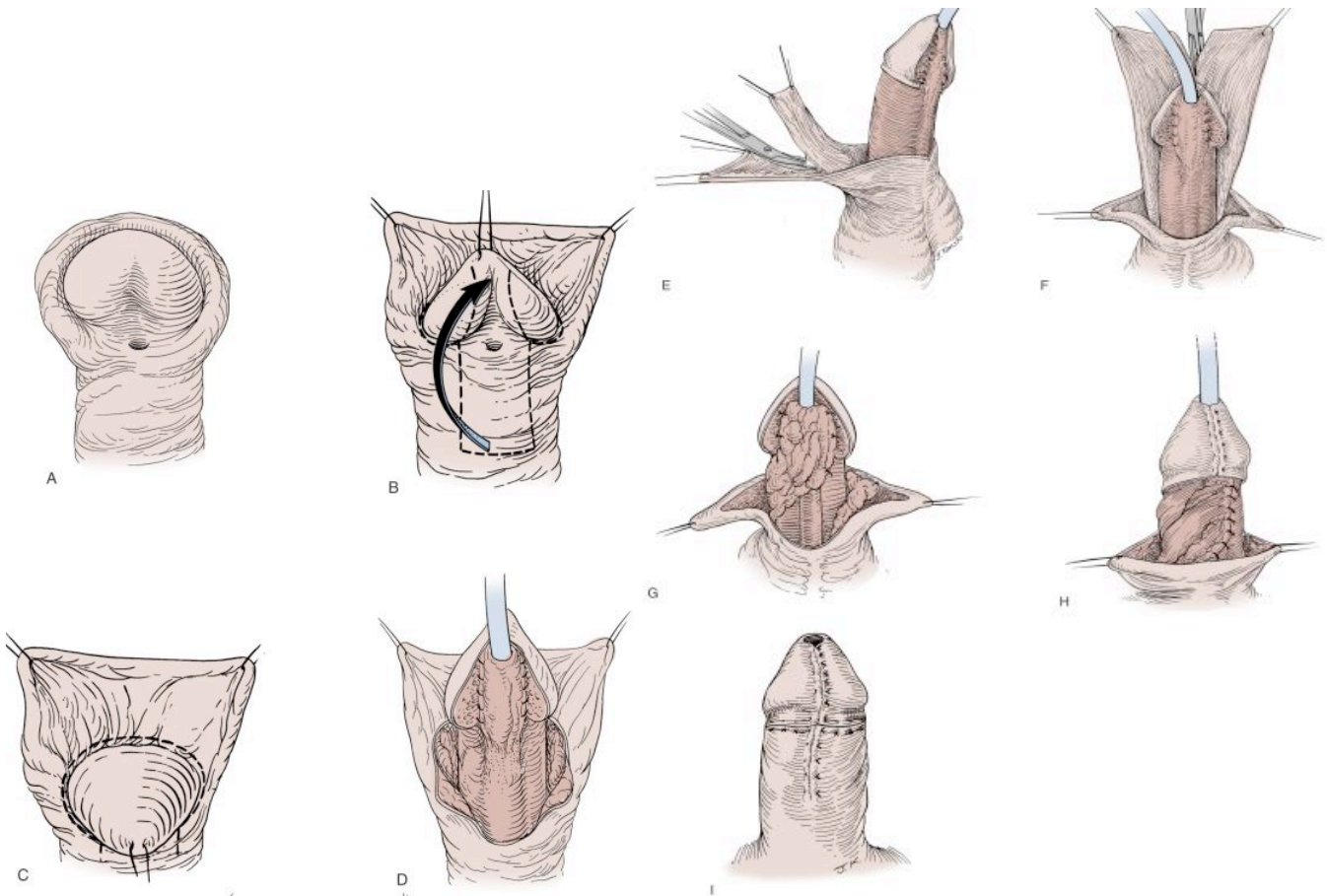
- stay suture placed in glans
- outline urethral plate depending on size of phallus } usually width of 7-9mm
- dilute epinephrine injected deep to proposed site of incision
- parallel longitudinal incisions made from tip of glans to hypospadiac meatus, demarcating the urethral plate
- transverse incision made across the skin overlying the urethra (proximally) to complete the U-shaped incision outlining the urethral plate
- circumcising subcoronal incision (5-7mm from coronal margin) made from each longitudinal incision
- penile shaft skin degloved
- orthoplasty PRN
- **longitudinal midline incision of urethral plate made from level of hypospadiac meatus to the tip of penis, as necessary**
 - depth of urethral plate incision depends primarily on configuration of glans and glanular groove
- urethral plate then tubularized over a 6Fr Silastic catheter with a running sc suture
- **wide meatus is fashioned**
- **2nd layer coverage of the neourethra with a well-vascularized sc dartos flap is harvested from the dorsal preputial and shaft skin**
- glans wings are approximated without tension in 2 layers
- indwelling silastic catheter secured to glans penis
- skin coverage completes repair



- DISTAL HYPOSPADIAS REPAIR } SNODGRASS TIP REPAIR
 } 3 CRITICAL STEPS
- LONGITUDINAL MIDLINE INCISION (C)
 - FORMATION OF WIDE MEATUS (E),
 - 2nd LAYER COVERAGE OF NEOURETHRA (F)

Describe the main steps of a Mathieu flap for distal hypospadias.

- measure length of defect } from urethral meatus to tip of glans
- equal length measured from meatus onto proximal penile shaft skin
- urethral plate and perimeatal-based flap are marked
→ usually 7.5mm at proximal end of flap which is tapered to 5.5mm at distal end of glans
- longitudinal lines outlining urethral plate drawn
- injection of dilute epinephrine
- circumferential subcoronal incision (5-7mm from corona of glans) made from lateral edges of marked urethral plate
- penile skin shaft is degloved
- glans wings are incised deeply
- orthoplasty PRN
- flap is elevated from penile ventrum in a proximal to distal direction
- flap is folded over at the meatus (perimeatal-based flap) and then sutured to urethral plate with running subcuticular sutures
- tubularization performed over a 6Fr Silastic catheter
- dorsal sc pedicled flap is harvested and divided in the midline
- one half of dartos flap is secured over neourethra
- maturation of meatus
- glans closed with sc simple sutures and skin closed with mattress sutures



→ DISTAL HYPOSPADIAS REPAIR } MATHIEU FLAP

What are the different types of techniques used for MIDDLE HYPOSPADIAS repair?

→ DISTAL SHAFT, MIDSHAFT, PROXIMAL SHAFT

→ reoperation rates & complications rates higher with more proximal defects

→ TUBULARIZATION TECHNIQUES

1) **Snodgrass TIP urethroplasty**

- modification of Thiersch-Duplay for **distal & some middle hypospadias**
- involves longitudinal midline incision of urethral plate, fashioning of wide meatus, and 2nd layer coverage of neourethral with sc dartos flap
- good functional results } complication rate of 1-5% (for primary repair)

→ FLAP TECHNIQUES

2) **Mathieu flap**

- perimeatal-based flap technique
- for **coronal, subcoronal, & some middle hypospadias**
- requires adequate ventral penile shaft skin
- excellent functional results } complication rate of ~1%
- cosmetic result is variable

3) **Onlay Island Flap (OIF)**

- for **distal shaft & midshaft hypospadias**
 - being used for even more proximal defects
- onlay segment harvested in transverse orientation and transferred ventrally
- requires intact urethral plate and correction of chordee with dorsal plication method
- re-operation rate is ~9% } 6% fistula rate

4) **Split Prepuce In-situ OIF**

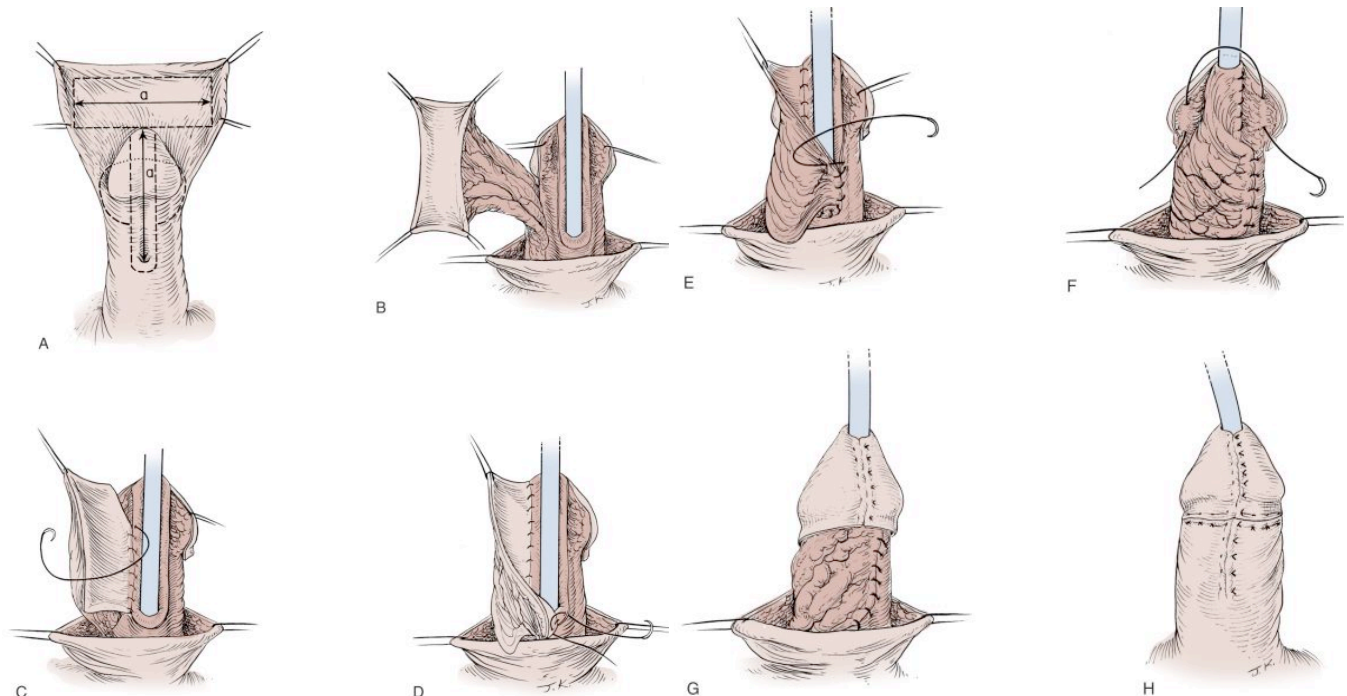
- modification of standard OIF
- for **distal shaft & midshaft hypospadias**
- onlay segment harvested in longitudinal orientation and transferred ventrally
 - preservation of whole blood supply to one half of prepuce
- re-operation rate is only 5% } 4% fistula rate
 - optimized blood supply to onlay flap

5) **Gonzalez Double-Onlay Preputial flap**

- modification of standard OIF
- **mainly for proximal hypospadias**
 - also used for **midshaft & proximal shaft hypospadias**
- preputial onlay segment harvested transversely and transposed ventrally with a "buttonhole" in the vascular pedicle
- preserves urethral plate BUT ALSO avoids the need for separation of the inner & outer preputial layers and the need for separate skin coverage of the onlay segment

Describe the main steps of an OIF repair for middle hypospadias defects.

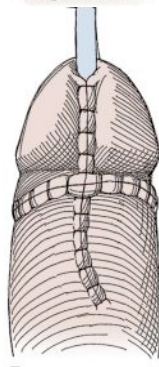
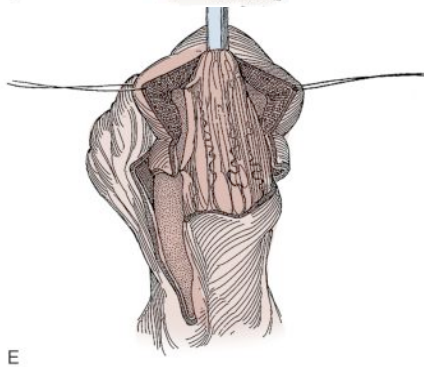
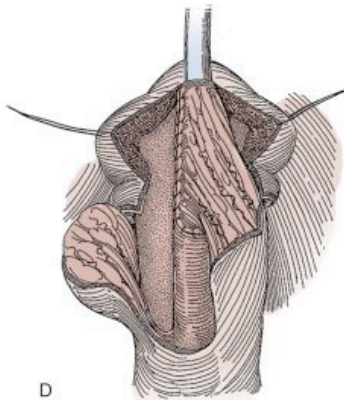
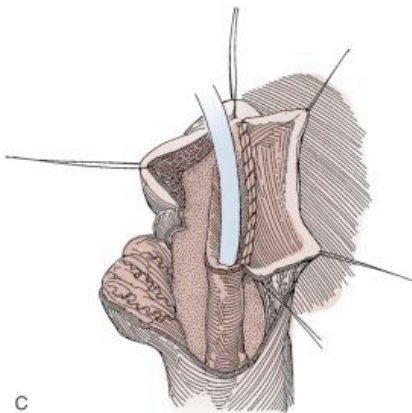
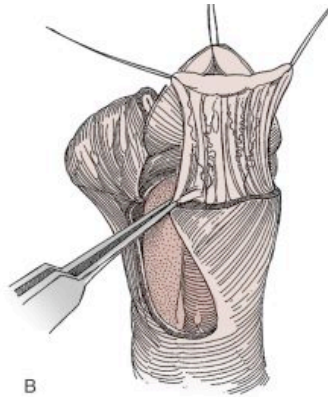
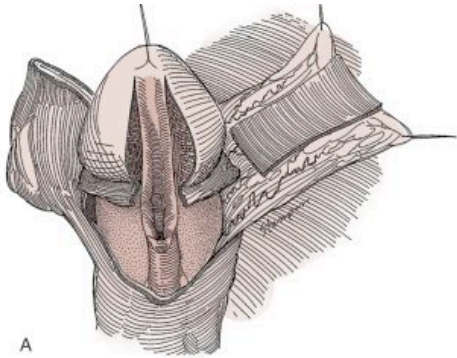
- traction suture placed in glans and fine stay sutures placed at corners of prepuce
- urethral plate is measured to a width of ~6mm
- parallel longitudinal incisions outlining the urethral plate are marked from hypospadiac meatus to glans tip
- injection of dilute epinephrine
- circumferential incision in distal penile shaft is made from lateral edges of urethral plate
- urethral plate incisions made
- orthoplasty PRN
- length of urethral meatus to tip of glans is measured
- same length is harvested as a rectangular onlay from preputial skin } usually 9-10mm width
 - preputial onlay is dissected with its pedicle from the outer preputial layer and dorsal penile shaft skin
 - dissection of pedicle to base of penis minimizes torque on penis and tension on repair
- rectangular OIF is passed around the penis to the ventrum
 - make sure onlay flap reaches site of anastomosis without tension
- tubularization performed over a 6Fr Silastic catheter with full-thickness running 6-0 Dexon from proximal edge of flap (now longitudinally oriented) to urethral plate on ipsilateral side of flap transfer
 - rest of tubularization performed with running subcuticular suture
- 2nd layer coverage of neourethra with advancement of inferolateral border of onlay pedicle or tunica vaginalis flap
- maturation of urethral meatus
- Silastic catheter is secured to glans
- glans approximation and skin closure performed



→ MIDDLE HYPOSPADIAS REPAIR } ONLAY ISLAND FLAP (OIF)

Describe the main steps of a Split Prepuce In-situ OIF for middle hypospadias defects.

- stay suture placed in glans
- prepuce is split in dorsal midline and penile shaft skin degloved
- urethral plate outlined
- island onlay flap is harvested from one half of the split prepuce
- onlay flap sutured to urethral plate starting with a running 7-0 Dexon full thickness then completed with subcuticular running suture
- neomeatus matured
- edges of vascularized onlay pedicle are secured lateral to the neourethral suture line as 2nd layer coverage
- repair is completed with skin coverage and securing of 8Fr Silastic catheter to glans



→ MIDDLE HYPOSPADIAS REPAIR } SPLIT PREPUCE IN-SITU OIF

What are the different techniques used for 1-STAGE PROXIMAL HYPOSPADIAS repair?

→ PENOSCROTAL, SCROTAL, PERINEAL

→ ONLAY FLAP TECHNIQUES

1) OIF

- for **distal shaft and midshaft hypospadias**
 - **being used for even more proximal defects**
- onlay segment harvested in transverse orientation and transferred ventrally
- higher complication rate than when used for middle hypospadias defects
 - ~30% complication rate for proximal defects
 - lower fistula rate relative to TPIF

2) Onlay-Tube-Onlay urethroplasty

- modification of OIF
- for **severe proximal hypospadias**
- composed of central tubularized + distal and proximal onlay components
- onlay segment harvested from preputial skin alone (harvested transversely) or from same strip of penile shaft & preputial skin (harvested longitudinally)

3) Gonzalez Double-Onlay Preputial flap

- modification of standard OIF
- **mainly for proximal hypospadias**
 - also used for **midshaft and proximal shaft hypospadias**
- preputial onlay segment harvested transversely & transposed ventrally w/ “buttonhole” in the vascular pedicle
- preserves urethral plate BUT ALSO avoids the need for separation of inner & outer preputial layers & the need for separate skin coverage of the onlay
- ~20% complication rate requiring re-operation

→ TUBULARIZATION TECHNIQUES

4) Duckett Transverse Preputial Island Flap (TPIF) } aka “Duckett tube”

- **most common single stage tubularized repair for proximal hypospadias**
- inner preputial skin w/ vascular pedicle transferred ventrally for neourethra, which is separate from and followed by transfer of longitudinally split outer preputial skin
- modification of TPIF has been described
 - longitudinal midline incision and tubularization of urethral plate (like TIP), proximally, + repair of remaining defect w/ TPIF
 - shorter defect length needing TPIF
- similar complication rates as OIF } ~30% overall complication rate with a ~10-15% fistula rate

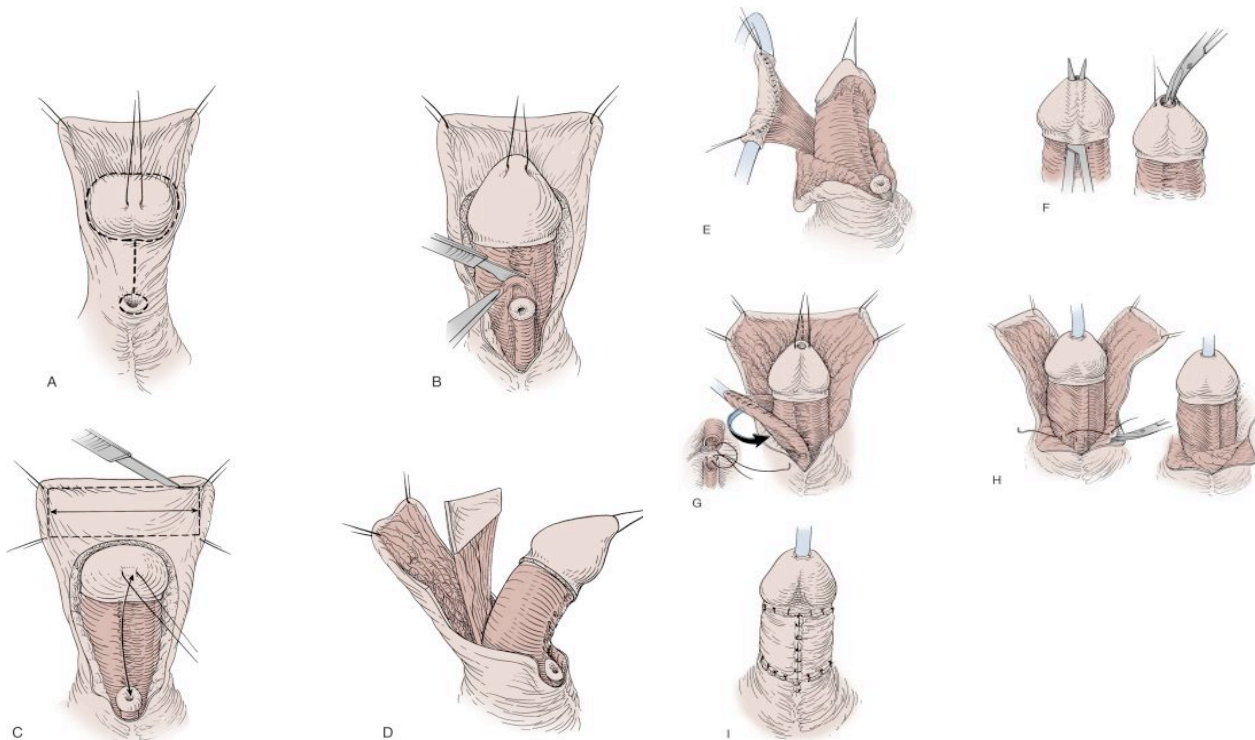
5) Koyanagi flap

- paramental foreskin flap
- use of strip of prepuce in continuity w/ longitudinal, ventral penile skin (“manta-wing flap”)
- complication rate ranges from 20-50%
- modification includes preservation of all dartos pedicle tissue with buttonhole transfer to ventrum and elimination of longitudinal incision in distal end of preputial collar

→ **RADICAL BULBAR DISSECTION** is a rapid adjunct applicable to all proximal hypospadias repairs to decrease severity of hypospadias needing defect & severity of chordee

Describe the main steps of a TPIF repair for proximal hypospadias defects.

- place fine traction sutures in glans and prepuce
- ventral midline longitudinal cut made from hypospadiac urethral meatus to distal circumcising incision
- penile shaft is degloved
- division of urethral plate PRN + ventral orthoplasty PRN
- length from urethral meatus to glans tip is measured
- same length of a transversely oriented rectangle of preputial skin is harvested } ~15mm wide
- once inner prepuce is dissected from outer layer of prepuce and dorsal penile skin, the flap is tubularized over a 6Fr Silastic catheter
- neourethral anastomosis made with running, subcuticular suture for 1st layer and then an inverting Lembert suture for 2nd layer
 - last 1cm of anastomosis is closed with simple, interrupted sutures to allow for future tailoring of the distal neourethral length
 - alternatively, preputial flap transferred & proximal anastomosis made before tubularization
- neourethral transferred to penile ventrum on tension-free pedicle
 - oriented so suture line is facing ventral surface of corpora cavernosa
- dorsal aspect of native meatus is fixed to ventrum of cavernosa before being anastomosed w/ neourethra
- small circular incision is marked in glans at proposed site of neomeatus
- wide channel is fashioned around 18Fr sound to accommodate passage of distal neourethra
 - core of glans tissue excised to achieve sufficient caliber
 - ALTERNATIVELY, can make deep midline incision in glans to allow advancement of neourethra and proper placement of meatus
- proximal anastomosis made first (running, locking full-thickness suture)
- distal end of neourethra is passed through glans channel and meatus is trimmed if necessary
- distal neourethra fixed to glans (simple, interrupted sutures)
- meatus matured
- dartos flap used as 2nd layer coverage of neourethra
 - can also cover with tunica vaginalis flap
- Silastic catheter is secured to glans & skin closed



→ PROXIMAL HYOSPADIAS REPAIR } ONE-STAGE DUCKETT TPIF

What are the different techniques used for **2-STAGE PROXIMAL HYPOSPADIAS** repair?

→ majority of proximal hypospadias defects can be managed with 1-stage repair

→ **preferred for scrotal or perineal hypospadias + severe chordee + small penis**

→ FIRST STAGE

→ **orthoplasty + transfer of healthy tissue to ventral shaft**

- stay sutures placed in glans and preputial skin
- ventral midline incision made from hypospadiac meatus to circumcising incision
- orthoplasty performed 1st } eg transverse incision of corpora cavernosa +
interposition dermal graft inlay
- glans incised deeply in ventral midline from circumcising incision distally to point of eventual neomeatus
 - ALTERNATIVELY, could leave glans intact and cover ventral shaft with approximation of prepuce to subcoronal circumcising incision then perform TIP urethroplasty for distal neourethra at 2nd stage
- midline longitudinal incision made in preputial & dorsal distal penile shaft skin
- each half brought around ventrally and anastomosed to ventral aspect of penis beginning at distal apex of glans incision (fine, interrupted absorbables)
- approximate transferred skin in ventral midline and to native meatus proximally (simple, interrupted sutures)
- in some cases, it may take all of the preputial skin to cover the ventral aspect of the liberated and straightened shaft

→ SECOND STAGE

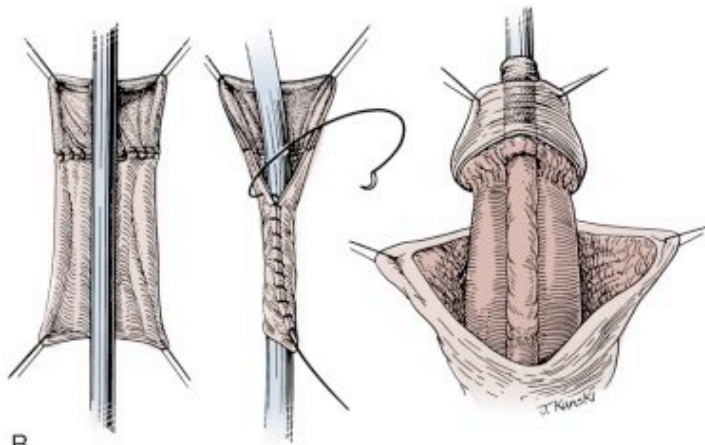
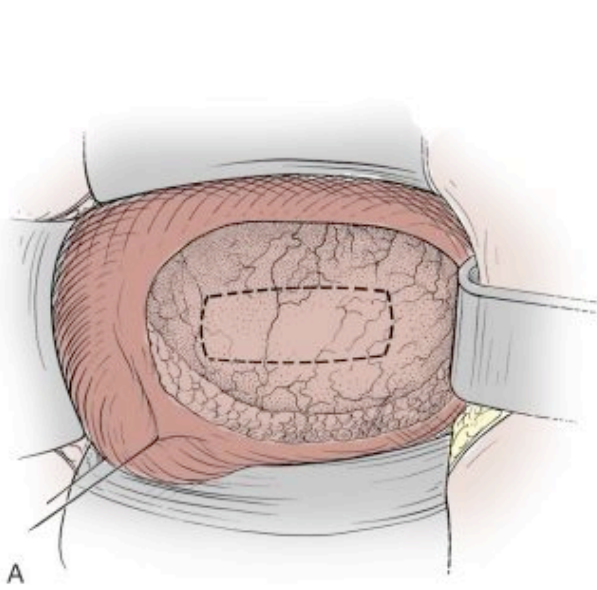
→ **performed ≥6 months after 1st stage**

→ **urethroplasty, meatoplasty, glanuloplasty, skin coverage**

- 1) tubularization of local skin in Thiersch-Duplay fashion
 - tissue used for neourethra is marked out on ventral aspect of penis with a width of ~15mm (centered on midline)
 - incise lateral edges of neourethral tissue but only dissect minimally toward the midline to preserve vascular supply to neourethra
 - neourethra tubularized (running subcuticular) & neomeatus secured to glans
 - 2nd layer coverage provided by either local subcutaneous dartos tissue flap or a tunica vaginalis flap
 - skin closed over neourethral and 2nd layer coverage
 - urinary diversion is with urethral catheter +/- S/P tube
- 2) free graft neourethra
 - use of non-hirsute skin, bladder or buccal mucosa } alone or in combination
 - buccal mucosa does not tend to shrink like bladder mucosa
 - bladder mucosa has higher chance of meatal stenosis
 - mucosal grafts have better outcome if used in onlay fashion (vs tubularized)
 - graft harvested and tubularized over 6Fr Silastic catheter
 - alone or as composite graft with skin and/or buccal mucosa
 - proximal anastomosis performed with 2 running, locking sutures
 - neomeatus matured with simple, interrupted, absorbable sutures
 - 2nd layer coverage provided by either dorsal dartos sc flap or by tunical vaginalis flap
 - urinary diversion is with urethral catheter + S/P tube

How is bladder and buccal mucosa harvested?

- bladder } bladder distended with saline and detrusor muscle dissected off underlying mucosa
 - } rectangular donor site harvested (10% greater than size of defect)
 - if combined with distal tubularized skin or buccal mucosa, can take 1:1
- buccal } GA with nasotracheal intubation
 - } diluted epinephrine injected submucosally
 - } appropriate-sized graft taken from mucosa of cheek and/or lip
 - avoid Stensen's duct
 - mucosa harvested superficial to buccinator muscle
 - } buccal mucosal edges are re-approximated with 5-0 chromic



B

→ 2ND STAGE OF 2-STAGE PROXIMAL HYPOSPADIAS REPAIR } BLADDER OR BUCCAL MUCOSAL
FREE GRAFT

COMPLICATIONS

List potential complications following hypospadias repair } ~5% for primary repairs

→ PERI-OP

- bleeding/hematoma } **most common complication**
 - } significant hematoma can lead to infection or repair breakdown
 - } think about bleeding disorder if excessive bleeding
 - Rx → start with compressive dressing
 - may require exploration & evacuation of hematoma
- wound infection } uncommon
 - Rx → if suspected, culture, add ABx, I&D prn, and debride prn
- breakdown of repair } **due to ischemia of local tissue or graft/flap, repair under tension, excessive cautery use, hematoma formation**
 - Rx → need to debride all necrotic tissue before repair
- urinary retention } if no catheter used

→ DELAYED

- meatal stenosis } **usually due to technical issue** (eg making urethral meatus with too narrow a lumen or performing a glanuloplasty too tight)
 - Rx → meatal dilation/meatotomy for mild cases
 - Rx → may need extensive flap procedure if concomitant complex distal urethral stricture
- urethrocutaneous fistula } **may be associated w/ distal urethral stricture, meatal stenosis, tissue ischemia, failure to add 2nd layer coverage, and/or failure to invert epithelial edges**
 - } **2nd layer coverage of neourethra has significantly reduced rate of fistula**
 - Rx → larger or multiple fistulae may require incision of intact skin bridges + delayed repeat repair
- urethral stricture } more common with proximal hypospadias repairs (eg TPIF)
 - Rx → 50% successful treatment by cold knife VIU
 - Rx → extensive stricture may require free graft or vascularized flap
 - results better if onlay (vs tubularized)
 - ~85% success rates
 - mucosal graft or meshed STSG are other options
- urethral diverticulum } uncommon
 - } **may be associated with distal stricture or meatal stenosis**
 - Rx → repair by circumferential skin incision + degloving, diverticular excision, urethral closure, & “pants over vest” sc tissue coverage
- recurrent chordee } likely due to either extensive fibrosis of reconstructed urethra, corporeal disproportion, or both
- BXO } may present with difficult micturition, meatal stenosis, or neourethral stricture
 - Rx → repair should involve use of bladder or buccal mucosal free grafts
- intraurethral hair } only occurs when hirsute skin is used either as transferred skin or tubularization of proximal penile or scrotal skin
 - Rx → laser ablation of hair is treatment of choice

When is the ideal time to re-operate for complications post-hypospadias repair?

- bleeding, infection, or debridement } immediate re-exploration
- re-operation for all other complications should be **delayed for at least 6 months**

What is a hypospadias cripple?

- hx of multiple, unsuccessful hypospadias repair attempts, with significant resultant penile deformity
- very difficult because they require extensive repair amid scarred and devitalized tissue

RE-DO HYPOSPADIAS REPAIR

What are the general principles of re-do hypospadias repair?

→ **minimum wait time is 6 months after previous failed repair**

- no attempts at repair until all edema, infection, and/or inflammation has resolved
- RUG +/- VCUG may be needed in complex re-do hypospadias repairs
- assess adequacy of local tissue vs the need for extragenital tissue graft

What are the different approaches to re-do hypospadias repair?

1) immediately adjacent or local tissue flap

→ preferred choice when possible

a) TIP urethroplasty } excellent option

→ local, usually well-vascularized tissue w/ skin coverage and good cosmesis

→ ~90% success rate (cf >95% for 1° repair)

→ **complication rate is 15-30% } cf 1-5% for primary repair**
} consists mostly of fistulae

→ TIP ideal after failed Mathieu flap, OIF, and tubularized procedures

- because native vascularity of urethral plate has not been altered
- no need for additional skin flaps, so lack of preputial skin not an issue

b) OIF

→ ~15% complication rate } cf ~10% for primary repair

c) Mathieu flap

→ ~25% complication rate } cf 1% for primary repair

d) TPIF

→ ~25% complication rate

2) free graft with local or extragenital tissue

a) tubularized free skin graft urethroplasty

b) free graft buccal or bladder mucosa } buccal mucosa preferred when skin-deficient

→ onlay vs tubularized } onlay has better results

→ 1st stage buccal onlay + 2nd stage tubularization } 20-25% complication rate

→ for more severe re-do cases

3) 1st stage meshed STSG onlay + 2nd stage tubularization with tunica vaginalis flap

→ last resort for hypospadias cripples

LONG-TERM FOLLOW-UP

What are some of the long-term issues post-hypospadias repair?

1) gender identity issues

- hypospadias NOT associated with abN gender-role behaviour
- hypospadias DOES NOT interfere with development of gender-typical masculine behaviour
- if posterior hypospadias +/- UDT then must r/o intersex state & effects of errors in T metabolism

2) cosmesis

- ~40% of kids & adolescents desire functional and/or cosmetic penile improvement

3) psychosexual issues

- hypospadias patients more likely to have negative genital appraisal
- hypospadias patients 2x more likely to avoid seeking sexual contact

4) urine flow

- uroflowmetry is valuable in identifying asymptomatic urethral strictures in some pts
- low flow rates often seen post-TIP urethroplasty

5) sexual function & fertility

- relatively N adult sexual function and fertility
- less sexually active, have a smaller # of partners, and seem to be less satisfied with their sex life

CURRENT TRENDS

What are some current trends in hypospadias repair?

- 1) **preservation of urethral plate, if possible**
→ increasing use of several tubularization & onlay techniques that preserve urethral plate
- 2) **completion of repair in 1-stage whenever possible**
→ **2-stage repair for very severe hypospadias & re-do cases**
- 3) use of SIS interposition graft to correct severe chordee is gaining popularity
- 4) TIP urethroplasty gaining popularity for primary & re-do repairs of distal & middle hypospadias
→ increased TIP urethroplasty for re-do hypospadias repairs may decrease need for extragenital tissue in this setting
- 5) OIF also being used more often
→ lower rate of fistula relative to TPIF
→ Split Prepuce In-situ Onlay variation of OIF also becoming popular
- 6) **preference for onlay (vs tubularized) techniques**
- 7) **increased use of pedicled, vascularized onlay flaps rather than free grafts**
- 8) for hypospadias w/ deficient ventral skin, buccal mucosa is preferred material for reconstruction

FUTURE CONCEPTS

What is the role of tissue-engineered constructs in hypospadias repair?

- use of extragenital donor tissue increases morbidity of surgery and/or length of stay
- potential is seen with human cadaveric, bladder submucosal, collagen-based inert matrix
→ Atala et al

Chapter #126 – Penile and Scrotal Abnormalities

NORMAL GENITALIA AND ASSOCIATION WITH OTHER ABNORMALITIES

What are the main causes of genital anomalies?

- disorder of sexual differentiation
- disorder of genital differentiation
- disorder of genital growth
- most recognized at birth; some detected in utero

What are the main embryologic features of genital differentiation?

- **cloacal folds (swellings)** form on either side of cloacal membrane
 - cloacal folds meet just anterior to cloacal membrane to form genital tubercle
- **undifferentiated until 7th week**
- males } occurs between weeks 9 and 13
 - } requires production of T by testes (Leydig cells) + conversion of T to DHT by enzymatic influence of 5 α -reductase
 - } DHT causes differentiation
 - 1) genital tubercle → glans penis
 - 2) genital/urethral folds → shaft of penis & penile urethra
 - 3) genital swellings → migrate inferomedially fusing in midline to become scrotum
- females } absence of testosterone and DHT
 - } passive differentiation
 - 1) genital tubercle → clitoris
 - 2) genital folds → labia minora
 - 3) genital swellings → labia majora

What are the 3 main mechanisms that can result in female genital differentiation in a XY male?

- 1) abN fetal T production
- 2) 5 α -reductase deficiency
- 3) androgen receptor (AR) defect

What is the N penile length at birth?

- full-term M neonate has avg stretched penile length of 3.5cm
- early penile growth seen in first ~3months of life
 - inhibitory effect of maternal estrogens disappears
 - results in transient surge of T production by Leydig cells
- slow penile growth from then on until puberty
- adult male has avg stretched penile length of 13.3cm

What is the N size of the urethral meatus in boys?

- **10F until 3yrs of age**, then increases gradually to 14Fr by age 12
- ~30F as an adult

What is the N appearance of a male penis?

- fully developed foreskin } may have ventral deficiency associated with hypospadias
- median raphe on shaft } 10% have deviated raphe (usually to left)
 - } deviated raphe may be assoc'd w/ penile torsion or chordee + hypospadias
- urethral meatus at tip of glans } hypospadias or epispadias occurs in ~1 of every 250 males
- penis is straight } congenital ventral or lateral curvature affects 0.6% of male neonates

What is the Tanner classification of Sexual Maturity Stages in boys?
→ based on pubic hair, penis, testes

Table 126-2 -- Tanner Classification of Sex Maturity Stages in Boys

Stage	Pubic Hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Scanty, long	Slight enlargement; slightly pigmented	Enlarged scrotum, pink, texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

How common are external genital abnormalities in kids with congenital anorectal malformations?

→ **up to 50% of kids with anorectal malformations have urologic malformations**

- high imperforate anus } 30% have hypospadias, penile duplication, micropenis, or scrotal deformities
- low imperforate anus } hypospadias most common

What are some of the syndromes commonly associated with male genital anomalies (CHART)?

→ microphallus, hypospadias, ambiguous genitalia, and bifid scrotum

- | | |
|-------------------------------------|--|
| - anencephaly | - Pallister-Hall syndrome |
| - WAGR | - Prader-Willi syndrome |
| - bladder exstrophy | - Popliteal pterygium syndrome |
| - Borjeson-Forssman-Lehman syndrome | - Rapp-Hodgkin ectodermal dysplasia syndrome |
| - carpenter's syndrome | - Schinzel-Giedan syndrome |
| - CHARGE association | - Rieger syndrome |
| - cloacal syndrome | - Robinow syndrome |
| - Fraser's syndrome | - Johanson-Blizzard syndrome |
| - Smith-Lemli-Opitz syndrome | - Meckel-Gruber syndrome |
| - Triploidy syndrome | - Noonan syndrome |
| | - XXY, XXXXY |

MALE GENITAL ANOMALIES

Penile anomalies

What is the natural history of phimosis in kids?

- N physiologic phimosis exists at birth due to natural adhesions b/w prepuce and glans
- **by age 3 yrs, 90% of foreskins can be retracted**
 - due to smegma (epithelial debris) and intermittent penile erections
- <1% of males have phimosis by 17yrs of age

List 4 differences between physiologic & pathologic phimosis.

PHYSIOLOGIC	PATHOLOGIC
<ul style="list-style-type: none">- usually young age (<3yrs)- can't see meatus unless foreskin retracted- foreskin is pink, soft- usually no hx of infection	<ul style="list-style-type: none">- usually older- meatus/glans often visible even w/o retraction- foreskin is white, fibrotic/scarred- often hx of recurrent balanoposthitis

What are the management principles of pediatric phimosis?

- 1) **early forceful retraction NOT recommended**
 - can lead to recurrent adhesions due to de-epithelialized glans
- 2) in boys >4-5yrs of age with persistent phimosis complicated by balanitis or balanoposthitis can use **topical corticosteroid cream tid x 6wks**
 - loosens phimotic ring in 70-80% } does NOT separate preputial adhesions
 - if phimosis recurs, can try 2nd course of steroid cream
- 3) phimosis in older boys may be due to BXO (40% of cases)
 - can also try course of topical steroid cream
- 4) Cx recommended only after failure of conservative Rx
 - use of local anesthetic is recommended by AAP
 - local block is better than just EMLA } risk of methemoglobinemia w/ EMLA

What are the indications for circumcision for phimosis?

- preputioplasty is also an option
- 1) boys >7-8 yrs of age with phimosis refractory to topical steroid cream
- 2) ballooning of foreskin with recurrent balanitis
- 3) recurrent UTIs in setting of phimosis

What are the pros & cons of circumcision?

PROS	CONS
<ul style="list-style-type: none">- prevention of penile cancer- prevention of UTIs in 1st yr (NNT = 11)<ul style="list-style-type: none">(mainly in boys w/ UTI hx)- may decrease STDs including HIV, HPV<ul style="list-style-type: none">(less cervical Ca in partners)- decreased risk of balanitis- decreased risk of phimosis/paraphimosis	<ul style="list-style-type: none">- surgical procedure (trauma) + potential complications- incidence of penile cancer rare- risk of UTI overall is still fairly low- ?long-term sexual dysfunction (unlikely)

When is circumcision contraindicated? }}} "Hebrew's Bris WISH ... Do Cx"

- Hypospadias
- Bleeding disorder
- Webbed or hidden penis
- Illness or jaundice
- Small penis
- Hydrocele or hernia (large) } more likely to develop 2° phimosis and a buried penis
- Dorsal hood deformity
- Chordee without hypospadias

What is the American Association of Pediatrics (AAP) position on neonatal Cx?

- potential medical benefits and advantages } need to discuss risks and benefits with parents
- AAP DOES NOT RECOMMEND ROUTINE CIRCUMCISION
- use of local anesthetic recommended for Cx

What is the Canadian Pediatrics Society (CPS) position on neonatal Cx?

- “routine neonatal circumcision should not be performed”

What are the potential complications of circumcision?

→ **complication rate for neonatal Cx is 0.2% to 3%**

→ early

- bleeding } usually from frenulum
 } usually controlled by compression but may need silver nitrate stick or ophthalmic cautery or rarely a suture
- wound infection } rare
- penile adhesions } common and usually resolves
- removal of excessive or insufficient skin } if too much removed, most will grow back
 → skin graft will disfigure penis
 } if too much left, revision may be needed
- penile or urethral injury } rare but often serious
 } partial glans removal should be sutured back immediately
 } penile necrosis can result from thermal injury

→ late

- meatal stenosis } usually get membranous web across ventral aspect of meatus
- } from severe meatal inflammation & scar formation post-Cx
- } **most common**
- } can also result from BXO
- skin bridge } don't resolve and needs excision
- secondary phimosis } can get trapped or buried penis
- buried/trapped penis/penile torsion
- chordee
- urethro-cutaneous fistula
- inclusion cysts

What is the management of inadvertent injection of epinephrine into the penis?

→ causes severe penile vasoconstriction

- 1) local infiltration with 0.4mg of phentolamine
- 2) insertion of caudal block (sympatholytic)

How does meatal stenosis present in kids?

→ doesn't usually become apparent until after kid is toilet trained

→ congenital (hypospadias) vs iatrogenic (post-Cx or post-hypospadias repair) vs BXO-related

- fine, forceful stream with great casting distance
- dorsally deflected stream
- prolonged voiding time

Rx → meatal dilation +/- steroid cream

→ meatoplasty +/- steroid cream

How does one counsel a parent regarding neonatal Cx?

- history and P/E
- give AAP and CPS statements
- discuss pros & cons
- describe procedure and potential complications
- describe expected recovery
- ask if there are any questions

What are the different types of penile cysts?

- 1) **smegma cyst } most common penile cyst**
 - } smegma trapped under phimotic foreskin
 - Rx → leave alone, foreskin will retract on own in most cases
- 2) congenital epidermal cyst } form along median penile raphe along shaft
 - Rx → simple excision
- 3) epidermal inclusion cysts } form after Cx, hypospadias repair, etc (trapped epithelial island)
 - Rx → simple excision

What is the management of an “inconspicuous penis”?

- 1) webbed penis } when scrotal skin extends onto ventrum of penis
 - } congenital or iatrogenic (post-Cx, etc)
 - } in rare cases, distal urethra is hypoplastic and may need reconstruction
 - Rx → incision of web transversely with closure of skin vertically
 - may need Byars’ preputial skin flap transferred to ventral surface
 - anchoring of scrotum to base of penis to prevent recurrence
- 2) buried penis } normal penis camouflaged by suprapubic fat pad
 - } congenital (inelasticity of dartos fascia) or iatrogenic (post-Cx, etc)
 - } usually have dysgenic bands on dorsal aspect of penis
 - Rx → type of surgery and timing of reconstruction is controversial
 - prn removal of dorsal dysgenic bands
 - unfurling of prepuce and use for penile shaft skin
 - fixation of dorsal aspect of penis to pubic fascia & scrotum to ventral aspect of base of penile shaft
 - may need to divide suspensory ligament of penis and excise SP fat
- 3) trapped penis } acquired form of inconspicuous penis
 - } can occur POST-Cx in baby w/ hydrocele, hernia, or webbed penis
 - } can lead to secondary phimosis and if severe, can cause UTIs and retention
 - Rx → fine hemostat dilation + steroid cream
 - correction under GA if severe and refractory to dilation + cream
- 4) micropenis } **N formed penis that is <2.5 SDs below the mean (ie <1.9cm in newborn)**
 - } usually have N ratio of length to girth
 - } may have severe hypoplasia of corpora cavernosa
 - } scrotum usually fused but small & testes usually small and undescended
 - } often associated with major chromosomal defects (eg Klinefelter’s)
 - } **true micropenis results from a hormonal abN’ity AFTER 14wks gestation**
 - if earlier, would result in differentiation issues + hypospadias also**

What are the causes of micropenis (CHART)?

- 1) deficient testosterone secretion
 - **hypogonadotropic hypogonadism (hypothalamic)**
 - isolated } including Kallmann’s syndrome
 - associated with other pituitary dysfxn } CHARGE
 - Prader-Willi, Laurence-Moon, Bardet-Biedl
 - **primary hypergonadotropic hypogonadism (testicular)**
 - anorchia
 - Klinefelter’s syndrome
 - Noonan’s syndrome
 - Down syndrome
 - incomplete gonadal dysgenesis
 - incomplete LH receptor defects
 - incomplete genetic defects in T steroidogenesis
 - Robinow syndrome
- 2) defects in testosterone action
 - GH/IGF-1 deficiency
 - incomplete androgen receptor defects
 - incomplete 5AR deficiency
 - fetal hydantoin syndrome
- 3) development anomalies
 - aphallia
 - cloacal exstrophy
- 4) **idiopathic**
- 5) associated with other congenital malformations

What is the management of a boy with micropenis?

- 1) pediatric endocrinology consult
→ need to identify endocrine abnormality if present
- 2) **karyotyping for all kids**
- 3) blood work
 - testosterone levels pre- and post-hCG stimulation
→ primary testicular if no response and basal elevated LH and FSH
 - serial measures of glucose, Na, K, cortisol, and TSH
- 4) MRI head to assess hypothalamus, anterior pituitary, and other midline structures
- 5) trial of androgen therapy +/- GH therapy
 - to determine end-organ response
 - im testosterone 25mg per month for 3/12
 - if penis DOES NOT respond to androgens, the question of gender reassignment is very controversial } used to recommend reassignment but now most recommend kids to be raised male
 - } most grow up w/ M gender identity & have satisfactory sexual function

What is penile torsion?

- rotational defect of penile shaft
 - usually rotated in **counter-clockwise direction (to the L side)**
 - usually have N penis size
 - may be associated with hypospadias or dorsal hood deformity without urethral abnormality
- Rx → correction mainly for cosmetic reasons
- usually unnecessary if rotation is <60-90 degrees from midline
 - if mild, may only need degloving + reorientation of skin and median raphe
 - if severe, may need degloving of penile skin + incision of dysgenetic bands near base
 - if still rotated may need tacking suture from corporal body to pubic symphysis

What is the management of lateral or dorsal curvatures of the penis?

- 1) lateral curvature
 - usually congenital } caused by overgrowth or hypoplasia of one corporal body
 - recognized later in life } penis N when flaccid

Rx → degloving + modified Nesbit procedure
- 2) dorsal curvature
 - congenital
 - usually have slender and long penis
 - some also have hypospadias

Rx → degloving + modified Nesbit (excision of ellipses from ventral corporal bodies)

What are the management options for paraphimosis?

- manual compression with distal traction works for most
- may need dorsal slit procedure
- other treatments described } iced glove for 5min, granulated sugar for 1-2hrs, multiple punctures in edematous skin

What is megaprepuce?

- severely redundant inner foreskin covering a normal glans penis
 - can't retract foreskin
 - get severe penoscrotal swelling with voiding and can get dysuria and UTIs
- Rx → degloving of penis + excision of redundant skin

What are the causes of priapism in kids?

→ **sickle cell disease (Hb SS) is the most common cause in kids**

- 25% of sickle cell disease kids develop priapism
- usually low-flow (ischemic)

→ ABG shows PO₂ <30 mmHg, PCO₂ >60 mmHg, and pH <7.25

- Rx → hydration, oxygenation, alkalization, exchange transfusion prn, pain meds
- AUA also recommends concurrent aspiration + irrigation (+/- phenylephrine)
 - consider shunts if refractory to meds + irrigation
 - oral α -agonist (pseudoephedrine) is 1st line for stuttering priapism
 - oral β -agonist (terbutaline) is 2nd line for stuttering priapism
 - GnRH analog + flutamide is 3rd line for stuttering priapism

→ high-flow/non-ischemic priapism less common

- usually related to perineal trauma (eg straddle injury) resulting in laceration of cavernous artery and development of a corporal fistula
- can also be due to Fabry's disease and sickle cell anemia

- Rx → observation (spontaneous resolution may occur)
- embolization if refractory to observation

What is genital lymphedema?

- disfiguring disorder characterized by impaired lymphatic drainage that causes progressive penile or scrotal swelling
- congenital or acquired
 - congenital } sporadic form(85%) is called lymphedema praecox
 - } inherited form (15%) is called Milroy's disease if occurring at birth and Meige's disease if occurring at puberty (AD inheritance)
 - } congenital form associated with Turner's, Noonan's, Klinefelter's, and intestinal lymphangiectasia syndromes

Rx → observation initially

- if lymphedema remains significant or progresses, surgical excision of all involved tissue
 - penis degloved and all tissue between Buck's fascia and skin is removed
 - all redundant penile skin excised
 - if scrotum involved, must excise most of scrotal skin

What is aphallia?

- **penile agenesis results from failure of development of the genital tubercle**
- rare (1 in 10-30 million)
- karyotype is **almost always 46 XY**
- well developed scrotum + descended testes + absent penile shaft + anteriorly displaced anus
 - urethra often opens at anal verge next to a small skin tag
 - sometimes it opens into the rectum
- **mortality rate is ~15%** } higher with more proximal urethral meatus
- } mortality rate almost 100% with vesicorectal fistula

Rx → gender assignment is controversial

- some will have a male gender identity
- need careful assessment by ambiguous genitalia team (surgeons, endocrine, psych, SW, etc)
- gender reassignment involves orchiectomy + feminizing genitoplasty as newborn with construction of neovagina at a later age

What malformations are associated with aphallia?

→ malformations are common

- horseshoe kidney
- renal agenesis
- VUR
- UDT
- imperforate anus
- MSK & cardiopulmonary abN'ities

What is diphallia?

- penile duplication is rare
 - ranges from small accessory penis to complete duplication
 - can sometimes have one corporal body + urethra per phallus
 - usually they are of unequal size and lie side by side
- Rx → imaging of urinary tract (ie MRI)
→ assess development of penis
→ individual treatment to obtain functional and cosmetic results

What anomalies are associated with diphallia?

- anomalies are common
- renal agenesis or ectopia
- bladder duplication
- hypospadias
- bifid scrotum
- diastasis of pubic symphysis
- anal & cardiac anomalies

What is chordee without hypospadias?

- N urethral + dorsal hood + variable degree of chordee
 - may have some ventral skin deficiency
- Rx → mild chordee } degloving + development of Byar's flap
→ severe chordee } may need dorsal plication, Nesbit dorsal excision, or corporal rotation
→ most severe cases } interposition island flap of dorsal foreskin needed

What is a congenital urethral fistula?

- rare anomaly
 - N urethra and meatus + urethrocutaneous fistula (typically coronal or subcoronal)
 - usually an isolated deformity
 - may be associated with imperforate anus, hypospadias, or ventral chordee
 - cause is unknown but likely involves some urethral plate defect
- Rx → fistula circumscribed and then closed in multiple layers
→ if the glans bridge is thin, can open into fistula and then close distal urethra by a Thiersch-Duplay tubularization or TIP technique

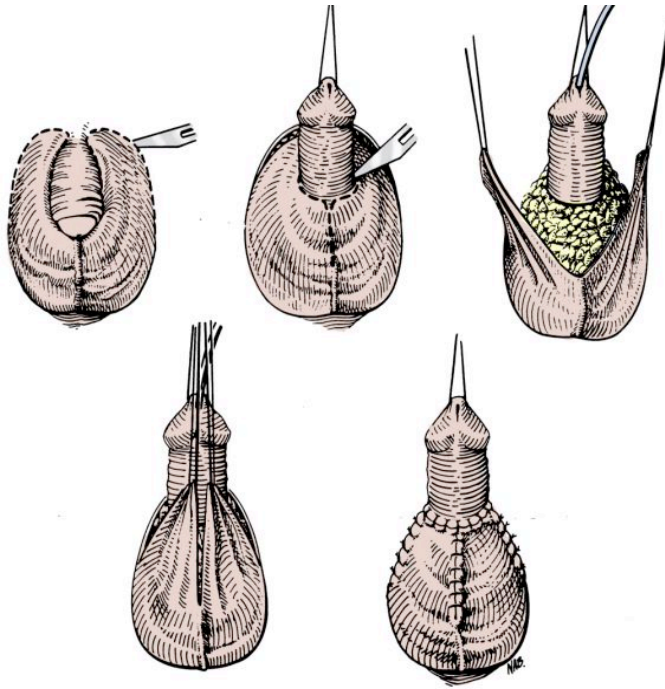
What are parametatal urethral cysts?

- rare anomaly
 - may be result of occlusion of paraurethral ducts or from faulty preputial separation from glans
 - cyst may consist of transitional and squamous as well as columnar epithelium
- Rx → simple excision

Scrotal anomalies

What is penoscrotal transposition (scrotal engulfment)?

- may be partial or complete
 - likely **results from incomplete or failed inferomedial migration of genital swellings**
 - often associated with proximal hypospadias (perineal, scrotal, or penoscrotal) + chordee
 - also associated with other syndromes
 - caudal regression
 - Aarskog syndrome
 - sex chromosome abN'ities
 - **if complete penoscrotal transposition + N scrotum then 75% have significant urinary tract abN'ity } should do U/S and VCUG**
- Rx → if normal penis, scrotoplasty can be done as outpatient
→ if associated hypospadias, then need 2 stage repair



What is an ectopic scrotum?

- anomalous position of one hemiscrotum along the inguinal canal
 - likely related to a defect in gubernacular formation
 - **usually suprainguinal**, but can also be infrainguinal or perineal
 - **associated with ipsilateral upper tract anomalies** especially when NO perineal lipoma is found
- Rx → scrotoplasty + orchidopexy

What anomalies are associated with an ectopic scrotum?

- UDT
- inguinal hernia
- exstrophy
- popliteal pterygium syndrome
- ipsilateral upper GU tract anomalies
 - renal agenesis
 - renal dysplasia
 - ectopic ureter
- perineal lipoma

What is a bifid scrotum?

- completely separated scrotum
- almost always associated with proximal hypospadias

What is scrotal hypoplasia?

- underdevelopment of one or both sides of the scrotum
 - occurs most commonly in boys with an UDT
- often noted in infants with genital ambiguity
- results from the lack of gubernacular swelling of the genital folds

What vascular lesions of the genitalia have been described?

1) hemangiomas

- present at birth and on the skin
 - may show significant growth in post-natal period but is followed by slow involution
- a) **cutaneous “strawberry” hemangiomas are the most common type**
 - from proliferation of immature capillary vessels
 - usually needs no treatment } tend to involute
 - } may need oral steroids, surgical excision, laser
 - b) subcutaneous “cavernous” hemangiomas
 - more like a vascular malformation
 - tends to enlarge gradually } use imaging to delineate true size (US, CT, MRI)
 - en bloc resection + pre-op embolization

2) vascular malformations

- present at birth but in subcutaneous tissues
- tend to persist or to enlarge
 - may expand due to trauma, sepsis, or hormonal changes
- slow-flow type } capillary, lymphatic, or venous
- fast-flow type } arterial, arteriovenous

What is the Klippel-Trenaunay-Weber syndrome?

- cutaneous vascular malformation (nevus flammeus) + soft tissue hypertrophy + bone hypertrophy
- triad present at birth that usually involves a lower extremity, trunk, or face
- ~30% have genitourinary involvement
- vascular lesions tend to bleed } excision is associated with significant blood loss

Miscellaneous Genital anomalies

What other genital anomalies have been described?

- 1) cysts of the median raphe

- can occur on perineum, scrotum, or shaft of penis
 - results from epithelial rests that become buried during urethral infolding
- Rx → excision if symptomatic or large

2) juvenile xanthogranulomas

- orange, gold, brown lesions that appear as one or more
- rapid onset
- can affect the penis

Rx → expectant management x 1yr minimum } most are self-limited

What genital manifestations can occur from meconium peritonitis?

- meconium hydrocele
 - congenital rupture of scrotum (scrotoschisis)
- suspect meconium peritonitis if an unusual inflammatory condition of the scrotum is detected

Chapter #127 – Abnormalities of the Testes and Scrotum

TESTICULAR EMBRYOLOGY AND NORMAL DESCENT

Describe the embryologic development of the testis & male sexual differentiation?

- chromosomal sex determined at time of fusion of gametes
- **male sexual differentiation does not start until testicular differentiation starts in week 7 by the SRY gene**
 - hormones from testes initiate and sustain N male development
 - lack of testicular hormones result in female sexual differentiation
- androgens (testosterone & DHT) mediate differentiation of the paired wolffian ducts into the epididymis, vas deferens, SVs, and ejaculatory ducts
- masculinization of external genitalia is also under similar influence of the testicular androgens
- 4-6 weeks } genital ridges organize followed by migration of primordial germ cells
- 7th week } **germ cells differentiate into gonocytes on entering the testicular cords to become fetal spermatogonia by 15 wks**
 - testicular differentiation
 - } **primitive Sertoli cells have developed as a result of SRY protein**
 - } gonadal ridges round off into an oval organ
 - } **gubernaculum (ventral ligament) appears and extends from gonad to fascia between developing external & internal oblique muscles**
- 8th week } **fetal testis starts to secrete T (Leydig cells) & MIS (Sertoli cells) independent of pituitary regulation**
 - this signals stabilization & differentiation of wolffian ducts and external genitalia and degeneration of mullerian structures
 - } testes are found adjacent to kidneys
 - } processus vaginalis develops
 - transversalis fascia (internal spermatic fascia), internal oblique (cremasteric muscle), external oblique (external spermatic fascia)
 - } **Leydig cells have differentiated**
 - } **testes remain intra-abdominally until ~23 weeks**
- 8-16 weeks } external genitalia develop in response to DHT
- testicular descent occurs between 24 to 34 weeks
 - 10% at 24 weeks
 - 50% at 27 weeks
 - 75% at 28 weeks
 - 80% at 34 weeks

THE UNDESCENDED TESTES

What is the cause of UDT?

- unknown
- multifactorial } not a single disease process with a common pathogenesis but a group of commonly recognized clinical abnormalities with multiple causes

What is the epidemiology of UDT?

- **isolated UDT is one of the most common congenital anomalies** } ~3% of full-term babies
- bilateral UDT is less common (1-2%) } ~25% of kids with UDT
- more common in premies & twins } **related to birth weight**
- more common among those **with +ve family hx** } 4-fold overall, 7-fold if brother with UDT
- **~75% will spontaneously descend by ~3 months of age**
- **at 1yr of age, the incidence of UDT is ~1%** } **remains constant throughout adulthood**
- **80% are clinically palpable**
 - significant portion of nonpalpable testes are palpable during EUA
- ~40% of kids with a nonpalpable testes are monorchid

What are the RFs for UDT? }}} “Undescended Balls, Family Please ACCEPT Son”

→ patient factors

- Under-weight (**low birth weight**)
- Small-for-gestational age
- Pre-term
- Twin neonate
- Family Hx +ve
- Congenital malformations
- Asian background

→ maternal factors

- Pre-eclampsia
- Breech presentation
- C/S delivery
- Estrogen, DES, etc exposure

What factors predict complete spontaneous descent of UDT by 3 months of age?

- low birth weight (**most important**)
- bilateral UDT
- N scrotal anatomy
- lower position along normal path of descent
- black or Hispanic
- family hx of UDT

What is the classification of UDT?

→ most accurately assessed on EUA

- 1) non-palpable (20%)
 - a) intra-abdominal } usually just inside the internal ring
 - b) peeping
- 2) palpable (80%)
 - a) intra-canalicular
 - b) extra-canalicular } suprapubic or infrapubic
 - c) ectopic } majority make it out external ring

What are some common locations for an ectopic testis?

- **Denis-Browne pouch (most common)** } between external oblique fascia & Scarpa's fascia
- prepenile ectopia
- transverse scrotal
- perineal
- femoral
- peri-hepatic & peri-splenic (rare)

What is implied by a “non-palpable testis”?

- intra-abdominal
- absent (vanishing) testis
- atrophic
- missed on P/E

What is a “retractile testis”?

→ **variant of normal**

- easily brought down to dependent position in scrotum & remains there after release of traction
- moves spontaneously out of scrotum toward inguinal canal by overactive cremasteric reflex
- **has been associated with abN testicular development, similar to UDT**
- risk of delayed spontaneous ascent up to 50%
 - delayed ascent likely represents UDT that was almost completely descended
 - **kids with “retractile testes” should be monitored yearly until puberty to r/o development of UDT**

What is the definition of testicular ascent?

→ any testis documented to be scrotal then **later found to be undescended**

→ 4 types

- infantile (true) } true UDT with patent hernia
- childhood (true) } nearly all have patent processus vaginalis (short cord structures)
- ectopic } most common form
 - } ectopic attachments allow testis to hang into scrotum but w/ linear growth testis ascends to ectopic position
- post-inguinal hernia repair } cord or testis caught up in scar tissue
 - } with linear growth, testis becomes undescended
 - } will not descend spontaneously or with hormones

What are the steps in normal testicular descent?

→ testes found **near kidneys at 8 wks** } **descent doesn't start until ~23 wks**

→ held by cranial suspensory ligament (CSL) & ventral suspensory ligament (gubernaculum)

- transabdominal descent } due to differential growth of lumbar vertebral column & pelvis
 - transinguinal descent } requires testis to travel through inguinal canal alongside & posterior to processus vaginalis into the scrotum
 - extracanalicular descent } occurs after ~28 wks and is complete by 30th - 32nd wk
- **CONTROVERSY** remains regarding the mechanism of descent

What are the histologic changes seen in an UDT?

→ the higher the undescended testis, the more pronounced impairment in germ cell development

→ **BUT**, newborns with intra-abdominal testes have a N number of germ cells

- histopathologic hallmarks associated with UDT are evident between 1-2 yrs of age

- decreased # of Leydig cells** } **first abN'ity seen postnatally**
- degeneration of Sertoli cells
- delayed disappearance of gonocytes
 - should transform into Ad spermatogonia by 6 months of age
 - **critical step in germ cell maturation & proliferation**
- delayed appearance of adult dark (Ad) spermatogonia**
 - **critical for future fertility**
 - likely androgen dependent
- failure of primary spermatocytes to develop**
 - should start to develop from Ad spermatogonia at 3-4yrs of age
 - **critical step in germ cell maturation & proliferation**
- reduced total germ cell counts

→ **peritubular fibrosis seen after puberty**

→ similar pathology seen in contralateral descended testis, but to a lesser extent

→ supports theory of hypogonadotropic hypogonadism as cause of decreased fertility seen in males with unilateral UDT

What factors may affect testicular descent? } } } "GEGE-I"

→ testicular descent is a complex event mediated by both hormonal & mechanical forces

1) Gubernaculum

→ **major factor responsible for testicular descent**

- may act in 2 ways } guide into scrotum (does not pull testis into the scrotum)
- } wedge that swells & dilates the inguinal path

2) Endocrine

→ normal hypothalamic-pituitary-gonadal axis required for N testicular descent

a) Androgens

- **androgens do not mediate transabdominal phase of testicular descent**
- **required for inguinal & scrotal phases of descent**

b) MIS

- MIS secreted by Sertoli cells } levels surge in 1st yr, peak at 4-12 months, then decrease w/ age
- patients w/ UDT have no surge, levels are decreased
- **likely has no significant role in regulation of testicular descent**

c) Estrogens

- prenatal tx w/ DES associated w/ urogenital abnormalities
- impairs gubernacular development
- cause persistence of Mullerian duct structures

e) Descendin

- androgen independent factor → gubernacular specific growth factor
- believed to be secreted from the testis in androgen-independent fashion

3) Genitofemoral nerve (GN) and calcitonin gene-related peptide (CGRP)

- transection of GF nerve in rats causes UDT } CGRP is neurotransmitter in GF nerve
- androgens increase the # of GFN cell bodies & promote gubernacular migration
- androgen blockade (flutamide) inhibits masculinization of GFN & decreases its CGRP content

4) Epididymis

- unknown if epididymal abnormalities are the cause or result of UDT
- abnormality in epididymis found in up to 90% of UDT
- epididymis precedes testis into the scrotum

5) Intra-abdominal pressure

- conditions w/ decreased IAP are associated with UDT
 - prune-belly, cloacal exstrophy, omphalocele, gastroschisis
- **more significant role in transinguinal descent**

6) ?Differential abdominal growth

What are the causes of in utero testosterone deficiency?

1) decreased LH

2) impaired function of GnRH or LH receptors

3) loss-of-function mutations in proteins involved in testosterone biosynthesis

- 17 α -hydroxylase/17,20-lyase (CYP17) deficiency } 46, XY usually assigned F gender at birth
- 3 β -hydroxysteroid dehydrogenase type 2 deficiency } rare cause of CAH which causes undervirilization of 46, XY fetus
- 17 β -hydroxysteroid dehydrogenase type 3 deficiency } 46, XY w/ female phenotype or ambiguous genitalia
- 5 α -reductase type 2 deficiency } clinical spectrum varies from F phenotype to hypospadias

What are some GU anomalies associated with UDT?

- Wilms' tumour
- unilateral renal agenesis
- Prune Belly syndrome
- horseshoe kidney
- hypospadias
- PUVs
- abN epididymis
- abN vas deferens
- patent processus vaginalis

What is the Wolf-Hirschhorn syndrome?

- hemangiomas + UDT
- defect on chromosome 4

What are the consequences of UDT?

→ reasons that support surgical treatment

1) infertility

- UDT results in **impaired germ cell maturation**
 - gonocytes form adult spermatogonia by 6 months
- early orchidopexy can reverse histologic changes seen
 - degree of improvement & timing of surgery are controversial
 - may not change risk for subfertility
- **paternity rates are lower in men with previous B/L cryptorchidism BUT NOT in unilateral cryptorchidism**
 - ~90% paternity for unilateral vs 30-60% paternity for bilateral
 - paternity rates also did not correlate with age at orchidopexy
- monorchidism is NOT associated with decreased paternity rates

2) testicular malignancy

- **relative risk of testis Ca is 40x higher in men with UDT**
 - 10% of testicular tumours arise from undescended testicle
 - the higher the location of the UDT, the greater the risk for malignancy
- orchidopexy before puberty MIGHT decrease this risk (eg NEJM 2007)
- normal contralaterally descended testis also has ~3.5x higher risk of malignancy
- risk of cancer in contralateral UDT (B/L cryptorchidism) is ~15%
- **seminoma is the most common tumour that develops in UDT**
- CIS is found in 1.7% of patients with UDT
 - more common in intra-abdominal testes
 - no evidence for Bx at time of orchidopexy

3) hernia

- **patent processus vaginalis found in >90% of patients with an UDT**
 - usually closed by 1 month after birth
- higher incidence of epididymal anomalies associated with patent processus vaginalis

4) torsion

- increased risk of torsion in UDT
 - due to developmental anatomic abN'ity in testicular mesentery
- testicular Ca is more common in torsion of an UDT

5) trauma

- especially inguinal testis

6) hypergonadotropic hypogonadism

- from decreased T levels

What are the RFs for infertility in men with a history of UDT?

- increased FSH
- low sperm count
- parenchymal testicular suture at time of orchidopexy

What are the potential causes of an increased risk of malignancy in UDT?

- exposure to increased temperature
- intrinsic pathologic process affecting both testes (more likely)

What is the work-up of an UDT?

- 1) history
 - preterm & maternal hx (use of gestational steroids)
 - perinatal hx (?scrotal exam at birth)
 - previous medical & surgical hx of child (?amiodarone)
 - FmHx of UDT or other syndromes
- 2) P/E
 - abdominal exam } masses, bladder, etc
 - penis, scrotum, & inguinal canal exam } hypospadias, ambiguous genitalia, hernia, etc
 - lumbar spine exam
 - examination of N contralateral testis } **hypertrophy may suggest monorchia**
 - >2mL or >2cm in length
 - warm hands with lubrication, milking from internal ring to scrotum
 - examine possible ectopic areas also
- 3) imaging
 - overall accuracy for an UDT is only 44% } high rate of false -ve's
 - **NO ROLE FOR IMAGING**
- 4) lab investigations
 - if unilateral UDT, no further lab tests needed
 - if B/L UDT, consider tests to confirm presence of testis } FSH, LH, hCG stim test
 - if associated with proximal hypospadias or ambiguous genitalia must r/o intersex !!
- 5) EUA +/- surgical exploration (diagnostic laparoscopy OR inguinal exploration)

What is the chance that an UDT is an absent testis?

- 80% palpable
- 20% non-palpable } 50% intra-abdominal
 - } 30% atrophic
 - } 20% absent \ **50% with non-palpable UDT will be monorchid**
/ **(ie 10% of all with UDT are monorchid)**

What is the work-up of bilateral UDT?

- **if associated with hypospadias or ambiguous genitalia may represent a life-threatening situation and merits special consideration**
- **NEED TO R/O INTERSEX STATE**
- if male karyotype confirmed, must consider bilateral anorchia
 - if FSH is elevated (3x normal) in pre-pubertal male likely means bilateral anorchia
- if gonadotropins are N, consider performing hCG stimulation test
 - 5000 U divided into 6 injections over 3wk period
 - DHT, FSH, and LH levels measured after each injection
 - T production confirms presence of a testicle } can get false -ve test if Leydig cells are unresponsive to exogenous hCG
- **all boys w/ non-palpable testes + N gonadotropins still need surgical exploration, regardless of hCG stimulation test**
- presence of inhibin B likely means presence of at least 1 testicle

What are the 5 main principles when treating undescended testicles?

- 1) proper identification of anatomy, position, and viability of the UDT
- 2) r/o potential coexisting syndromic abN'ities
- 3) placement of testis within scrotum in timely fashion to prevent further testicular impairment (fertility function and endocrinologic function)
- 4) attainment of permanent fixation of testis within N scrotal position allowing easy palpation
- 5) no further testicular damage from Rx

What are the management options for UDT?

→ **definitive treatment should take place between 6 and 12 months of age**

1) hormonal therapy

- exogenous hCG or exogenous GnRH/LHRH } to increase serum testosterone
- success rate better with lower pre-treatment positions
- routine re-examination is needed after hormones } ~25% re-ascent rate
- hormones are NOT indicated if;
 - previous surgery that results in inguinal scar tissue
 - ectopic testes
 - those with inguinal hernia
- **overall success is <20%** for cryptorchid testes and is significantly dependent on pretreatment testicular location

2) surgery

→ procedure and success depends on location of testis (gold standard Rx for UDT)

→ **PALPABLE (80%)**

a) standard orchidopexy (inguinal vs scrotal)

→ for low inguinal or high scrotal testes

→ **4 principles of orchidopexy**

- **complete mobilization of the testis & spermatic cord**
- **repair of patent processus vaginalis by high ligation of hernia sac**
- **skeletonize spermatic cord w/o compromising vascular supply**
- **creation of superficial pouch within hemiscrotum**

b) Fowler-Stephens orchidopexy (single stage vs 2-stage)

→ for high inguinal or intra-abdominal testes

- relies on collateral blood supply to the testis
- if performing 1-stage, must preserve wide pedicle of peritoneum w/ vas to maintain collateral flow (do not disturb peritoneum medial to testis)
- 2-stage procedure allows for development of collaterals & for greater mobility of testis prior to placement within scrotum

→ **NON-PALPABLE (imaging alone is inaccurate)**

→ open inguinal exploration VS diagnostic laparoscopy (controversial – see later)

c) abdominal orchidopexy [standard vs Fowler-Stephens (single vs 2-stage)]

d) lap orchidopexy [standard vs Fowler-Stephens (single vs 2-stage)]

- has benefit of accessibility to entire length of spermatic vessels
- magnification allows for good visualization of main and collateral blood supply
- 1-stage vs 2-stage based on location of testis and mobility of testis

e) microvascular autotransplantation

f) orchiectomy

What are the S/E's of hormonal therapy for UDT?

→ NOT 1st line

- increased rugation & pigmentation of scrotum
- increased size of penis & development of pubic hair } rare and regresses after Rx
- transient decrease in # of lymphocytes } **avoid in immunosuppressed kids**

What is the role of microvascular testicular auto-Tx?

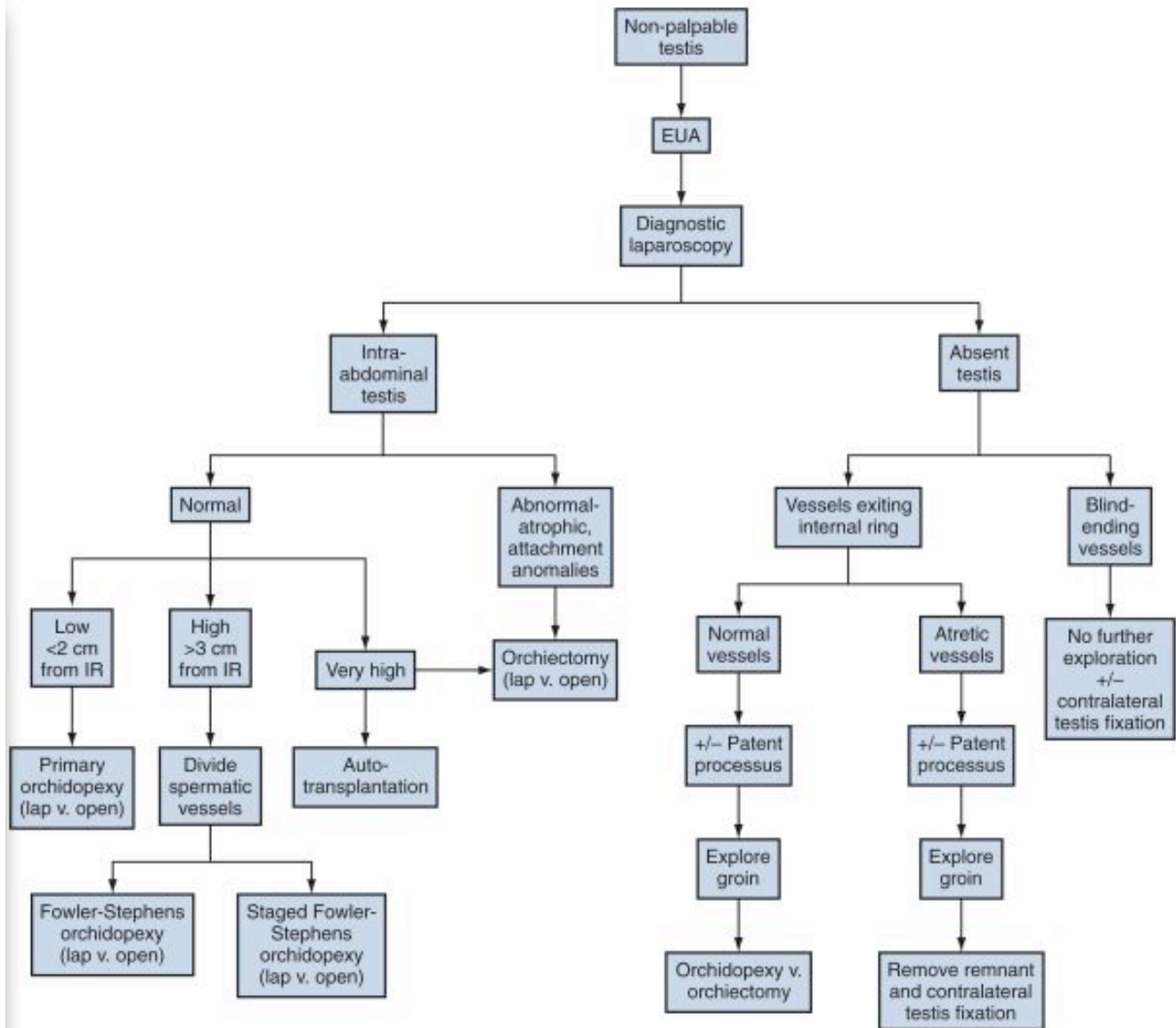
→ similar indications as those for a Fowler-Stephens orchidopexy

- **may be ideal for solitary, high intra-abdominal testis (via Gibson)**

- advocates say variability of collaterals in kids w/ high UDT may compromise result of Fowler-Stephens
- can give hCG before surgery to increase vascular caliber
- internal spermatic artery anastomosed to inferior epigastric artery } microvascular expertise NB

What are the indications for orchiectomy in UDT?

- postpubertal male with contralateral N descended testis
- postpubertal male with anatomically or morphologically abN UDT
- postpubertal male with testis that can't be monitored due to location
- pre-pubertal male with high intra-abdominal testis that can't be brought down



→ MANAGEMENT ALGORITHM FOR NON-PALPABLE TESTIS

Describe the main steps of a standard inguinal orchidopexy.

- transverse inguinal skin incision made in mid-inguinal canal
- open subcutaneous tissue and Scarpa's fascia
- clean external oblique fascia of prefascial fat
- define Poupart's ligament (Inguinal ligament) to help maintain anatomic orientation
- open external oblique fascia } watch out for ilioinguinal nerve
- grasp testis and sharply dissect the distal gubernacular attachments to free testis into wound
- cremasteric muscle fibers dissected off testis and spermatic cord
- once spermatic cord is mobilized to level of internal inguinal ring, tunica vaginalis is opened
- separation of patent processus vaginalis from spermatic cord and high ligation of hernia sac which usually lies anteromedial to cord
- transverse mid-scrotal incision and development of superficial dartos pouch
- testis brought down into scrotal incision
- testis secured to scrotum with interrupted sutures through tunica albuginea
 - avoid transparenchymal suture fixation } causes testicular damage
- dartos fascial window closed with absorbable suture
- scrotal skin closed
- external oblique fascia closed with running absorbable suture
- Scarpa's fascia and skin closed
- collodion dressing vs steri-strips

What is the blood supply to the testis?

- 1) testicular/gonadal artery (aorta)
- 2) vas deferential artery (branch of inferior vesical artery)
- 3) cremasteric artery (branch of inferior epigastric artery)

List methods to gain extra length of spermatic cord during orchidopexy?

- 1) complete mobilization of cremasterics off spermatic cord
- 2) high ligation of hernia sac
- 3) Prentiss maneuver
- 4) Jones incision (retroperitoneal dissection)
- 5) Fowler-Stephens procedure } see below

Describe the main steps of a Prentiss maneuver for UDT.

- incise floor of inguinal canal through external ring
- divide inferior epigastric vessels to swing cord medially
- testis passed through abdo wall (int. oblique) in a more medial location
- internal ring & transversalis fascia are closed lateral to the cord
- thorough retroperitoneal dissection of lateral attachments

Describe the main steps of a Jones incision for UDT.

- open surgical alternative for high canalicular testis
- transverse incision made medial to ASIS & carried down to external oblique fascia just superior to internal ring
- muscle-splitting technique used to expose retroperitoneum
- peritoneum mobilized medially & opened at level of internal ring
- hernia sac ligated & spermatic vessels dissected from lateral spermatic fascia as far cranial as possible
- Prentiss maneuver performed to pass testis under floor of inguinal canal to exit just above pubic tubercle

Describe the main steps of a Fowler-Stephens orchidopexy?

- high transverse inguinal incision made that can be extended laterally
- external oblique fascia opened to enter inguinal canal
- if present, hernia sac mobilized off cord to level of internal ring then opened
- identify testis and mobilize into incision } don't transect any proximal structures
- identify vessels to testis and vas deferens
 - **long, looping vas is most important requirement for successful Fowler-Stephens**
 - if present, can perform 1-stage repair
- vas is mobilized up from inguinal canal and protected
- spermatic vessels are divided high above testis once it has been determined testis will not traverse distance to the scrotum
 - can first perform Fowler-Stephens test } temporary occlusion of testicular artery
 - if testicular blood supply is tenuous, 2-stage Fowler-Stephens is preferred
- testis mobilized on wide swath of peritoneum with vas deferens
 - incision made in peritoneum lateral to testis } watch out for ureter
- testis passed through abdo wall over symphysis pubis or medial to inferior epigastric vessels (Prentiss maneuver)
- superficial dartos pouch made via transverse scrotal incision
- testis passed down into scrotum
- testis secured to scrotum with interrupted sutures through tunica albuginea
 - avoid transparenchymal suture fixation } causes testicular damage
- dartos fascial window closed with absorbable suture & scrotal skin closed
- external oblique fascia closed with running absorbable suture & Scarpa's fascia and skin closed
- collodion dressing vs steri-strips

What are the 3 possible findings on diagnostic laparoscopy for a nonpalpable testis?

- 1) **N vessels + vas entering internal ring** } missed viable intra-canalicular testis
VS remnant/nubbin outside internal ring
→ only 10-15% of remnants/nubbins have residual viable tissue BUT must perform open inguinal exploration
→ risk of Ca & viable testis function
- 2) **blind ending vessels above internal ring** } vanishing testis VS true testicular agenesis
- 3) **intra-abdominal testis** } usually found within few cm's of internal ring
} must decide on viability
} **patent processus vaginalis associated with a viable testis**

What are the Pros/Cons of open inguinal exploration vs laparoscopic exploration of nonpalpable testis?

	PROS	CONS
Open inguinal Exploration	<ul style="list-style-type: none"> - avoids laparoscopy if remnants, vessels, vas, etc were detected in inguinal canal - can perform inguinal laparoscopy 	<ul style="list-style-type: none"> - laparoscopy still needed if –ve open exploration and intra-abdominal testis is suspected
Diagnostic lap exploration	<ul style="list-style-type: none"> - avoids open surgical exploration if vanishing testis diagnosed - can perform therapeutic orchiectomy if nonviable intra-abdo testis - can assess feasibility of single or 2-stage orchidopexy - can assess contralateral anatomy 	<ul style="list-style-type: none"> - open exploration would have been needed anyway if vessels, vas, etc seen exiting internal ring

- controversial } mainly depends on where you think testis/nubbin/remnant/etc resides
 - if you think more common outside internal ring, go w/ inguinal exploration
 - if you think more common inside internal ring, go w/ exploratory laparoscopy

What is the significance of a “vanishing testis”?

- due to either an intra-abdominal or inguino-scrotal event
- Dx made by seeing **blind ending vessels** +/- vas, usually a few cm's from the internal ring
- no testicular tissue present
- **no further Rx**
- reported risk of bell-clapper deformity in contralateral testis } consider orchidopexy

Describe the main points of a laparoscopic orchidopexy.

- diagnostic laparoscopy performed
 - intra-abdominal testis usually found within 1-2cm of internal ring
 - **internal ring usually patent when intra-abdominal testis is viable**
 - **if testis >2.5 to 4cm from internal ring & immobile, perform staged orchidopexy**
- placement of 2 more ports
- start mobilizing testicle by drawing in gubernacular attachment from internal ring & transecting it to free up testicle
 - watch out for looping vas that dips into inguinal canal
- incision made in peritoneum at internal ring, lateral to spermatic vessels, & carried along abdo sidewall or psoas muscle parallel and cranial along pelvic sidewall toward bladder
- triangular wedge of peritoneum preserved b/w spermatic vessels and vas deferens, w/ testis at the apex
 - **if 1-stage Fowler-Stephens planned, need to preserve peritoneum between the spermatic vessels and vas (collateral vasculature)**
- dissection of peritoneum off posterior retroperitoneum until testis can be brought across and beyond the contralateral internal ring without tension
- testis transferred into scrotum
 - monitor tension on cord to avoid inadvertent avulsion of spermatic vessels
- if more length needed, dissect peritoneum overlying spermatic vessels as cephalad as possible
- subdartos pouch created via transverse scrotal incision
- testis sutured in place } may need fixation button
- no need to close internal ring } doesn't form clinical hernia post-op

Describe the main steps of a 2nd stage Fowler-Stephens orchidopexy?

- during initial procedure, internal spermatic vessels were clipped
- 2nd stage performed 6 months later
 - can be performed either open or laparoscopic
- spermatic vessels are divided
- peritoneal incision made wide and lateral to distal spermatic vessels and testis
- 2nd incision made distal to vas deferens
- testis mobilized on wide triangular swath of peritoneum
 - **be careful to preserve vasal artery and any collaterals**
- testis transferred into scrotum
- subdartos pouch created via transverse scrotal incision
- testis sutured in place } may need fixation button
- no need to close internal ring } doesn't form clinical hernia post-op

What are the principles of a re-do orchidopexy?

- skin incision & initial exposure should be in a non-operated area
 - dissection from normal to scarred tissue
- initial dissection toward lower pole of testis
- once testis is freed, care is taken when mobilizing cord } likely previously skeletonized
- dissection can be performed lateral and medial to the cord to lessen risk of injury to vessels

What are the potential complications of orchidopexy?

→ peri-op

- infection
- hematoma
- ilioinguinal nerve injury
- testicular artery injury (unless done on purpose – Fowler-Stephens)
- damage to the vas deferens
- post-op torsion
- complications of laparoscopy (if done laparoscopically)

→ late

- testicular atrophy
- testicular retraction
- hernia

What are the causes of testicular atrophy post-orchidopexy?

- skeletonization of cord
- excessive cautery use
- inadvertent torsion of vessels during passage down to scrotum
- ligation & division of testicular vessels during Fowler-Stephens orchidopexy (ie poor collateralization)
- excessive axial tension on testicular vessels

What is the success rate for orchidopexy?

→ success depends largely on location of UDT

- 1-stage Fowler-Stephens } 67%
- 2-stage Fowler-Stephens } 77%
- abdominal orchidopexy } 81%
- inguinal orchidopexy } 89%
- upper scrotal orchidopexy } 92%

HERNIAS AND HYDROCELES

What is the significance of a pediatric hydrocele?

→ **all pediatric hydroceles result from persistence or delayed closure of processus vaginalis**

- simple hydrocele } processus has obliterated (**doesn't fluctuate** in size throughout the day)
 - } commonly seen at birth
 - } often bilateral and may be large
 - } painless & transilluminates
 - } most resolve during first 2yrs of life

Rx → observation

- if repaired, take inguinal approach (patent processus may be present)
- aspiration contraindicated (risk of peritonitis if patent processus)

- communicating hydrocele } patent processus vaginalis
 - } congenital but may not present until older kid
 - } **changes in size (fluctuates)**, usually related to activity
 - usually larger at end of day
 - } variable consistency and may be soft or tense
 - } may be able to express fluid back into peritoneum
 - } must r/o UDT associated with communicating hydrocele

Rx → inguinal exploration } some recommend observation

- high ligation of hernia sac } open sac if any doubt
- close internal ring if patulous
- +/- scrotal orchidopexy prn } don't need to deliver testis in all cases

- **there is controversy re: exploration of contralateral N inguinal canal**

- hydrocele of the cord } simple vs communicating
 - } due to segmental closure of the processus vaginalis
 - } usually a mobile, painless groin mass contiguous with the cord
 - } **must r/o sarcoma of cord, paratesticular sarcoma, hernia**

Rx → inguinal exploration

- high ligation of patent processus at internal ring
- excision or unroofing of hydrocele

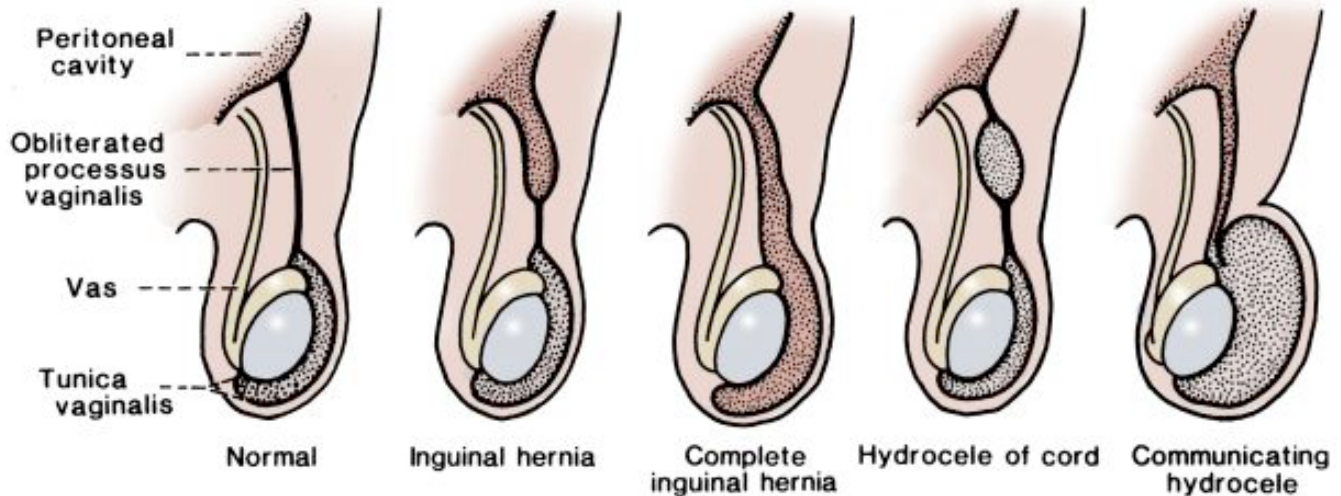
- abdominoscrotal hydrocele } large, bilobed hydrocele spans internal inguinal ring (rare)
 - large inguinoscrotal component + large intra-abdominal component
 - abdominal component is "spill over" from scrotal hydrocele
 - } palpable abdo mass
 - } compression of one component causes other to enlarge

Rx → inguinal exploration

- removal of entire abdominal component essential
- failure to do so is cause of recurrence

List the indications for exploration of the contralateral N inguinal canal after ipsilateral inguinal hernia or communicating hydrocele repair?

- no consensus re: need to explore contralateral N inguinal canal, the technique to use, or the age below which evaluation is recommended
 - 1) past or present hx of contralateral inguinal or scrotal pathology
 - 2) presence of VP shunt
 - 3) patient on PD



ACUTE SCROTUM

What is the DDx of an acute scrotum (CHART)?

- **testicular torsion**
- torsion of the appendix testis
- torsion of the appendix epididymis
- epididymitis
- epididymo-orchitis
- inguinal hernia
- communicating hydrocele
- simple hydrocele
- hydrocele of the cord
- tumour
- trauma/insect bite
- spermatocele
- varicocele
- skin lesions
- inflammatory vasculitis (Henoch-Schonlein purpura)
- idiopathic scrotal edema
- nongenital (adductor tendonitis)

How does testicular torsion usually present?

- history } acute onset of scrotal pain
 - may have hx of self-limited scrotal pain and swelling
 - can wake kids up from sleep
- } usually no LUTs
- } ++ N/V
- } can get referred pain to lower quadrant of abdomen
- P/E } high-riding testicle with transverse orientation
- } acute hydrocele or massive scrotal edema
- } **absent cremasteric reflex**
- **good indicator**
- **intravaginal torsion** may result from lack of N fixation of an appropriate portion of the testis & epididymis to the fascial & muscular coverings that surround cord
- bell-clapper deformity
- usually occurs close to puberty

What is the management of testicular torsion?

- irreversible ischemic injury can start as early as 4hrs (immature testis more fragile)
- 1) attempt at manual detorsion
 - opening book } **DOES NOT obviate need for scrotal exploration**
- 2) immediate scrotal exploration if high index of suspicion
 - exploration of affected side first
 - detorsion + placement in warm sponges + assessment of viability +/- orchidopexy
 - must remove necrotic testis
 - **exploration of contralateral testis if torsion found**
 - contralateral orchidopexy necessary as Bell-Clapper deformity found in most
 - antenatal torsion is extravaginal } need for contralateral orchidopexy debatable
- 3) Doppler U/S
 - very low false +ve rate
 - performed to confirm absence of torsion if another etiology is suspected

What is the management of intermittent testicular torsion?

- diagnosis made on hx
- elective exploration } scrotal orchidopexy if bell-clapper deformity is identified

What is the management of torsion of the testicular & epididymal appendages?

- appendix testis = mullerian duct remnant → appendix epididymis = wolffian duct remnant
- presentation can vary from scrotal discomfort to acute scrotum
- may have localized tenderness or “blue dot sign”
- testis should be mobile & cremasteric reflex still present
- can be confirmed on imaging, though not always accurate
- Rx → observation + NSAIDs
 - acute exploration if testicular torsion suspected
 - delayed exploration if failure of observation } simple excision of twisted appendage

What is the management of epididymitis in kids?

- uncommon in kids
- dysuria & fever more common than in torsion, although still not the rule
- more common if hx of UTIs, urethritis, urethral D/C, sexual activity, catheterization, GU tract surgery
- associated with Henoch-Schonlein purpura & amiodarone use
- **cremasteric reflex should be present**
- **pyuria, bacteriuria, or a +ve urine C&S should make epididymitis highly likely**
- may be related to dysfunctional voiding with VUR into ejaculatory duct
- Rx → ABx } iv if UTI suspected
 - bedrest/limited activity
 - avoid urethral instrumentation
 - if pre-pubertal & +ve urine culture, must perform abdo U/S + VCUG

What is the management of ANTENATAL testicular torsion?

- antenatal (in utero) torsion different from postnatal torsion
- **hard, nontender testis fixed to overlying scrotal skin at delivery**
- skin discolored by underlying hemorrhagic necrosis
- usually **extra-vaginal torsion** } **usually NOT associated with bell-clapper deformity**
- “vanishing testis” may be result of antenatal torsion
- Rx → observation of affected testicle + delayed orchiectomy (days to wks) + contralateral orchidopexy
 - exploration of contralateral testis controversial b/c extravaginal torsion (NO bell-clapper deformity)
 - **MOST WILL EXPLORE & PERFORM CONTRALATERAL ORCHIDOPEXY**

What is the management of POSTNATAL torsion?

- tenderness of the scrotum } scrotal reaction is later finding or may mean not torsion at all
- fixation of the skin is usually NOT present
- Rx → **immediate exploration of suspected postnatal torsion** } **consider inguinal approach**
 - if torsion is the Dx, must perform contralateral orchidopexy

VARICOCELE

What is a varicocele?

- ectatic & tortuous veins of the pampiniform plexus of the spermatic cord
- **found in ~15% of male adolescents** } rarely clinically evident before early adolescence
 - } not all varicoceles cause infertility
 - 40% in infertile men
- **90% L sided**

What is the DDx of a painless scrotal mass in an adolescent?

- varicocele
- inguinal hernia
- omental hernia
- communicating hydrocele
- simple hydrocele
- hydrocele of the cord
- spermatocele
- tumour

What is the etiology of varicoceles?

- likely multifactorial
 - 1) increased venous pressure in L renal vein
 - 2) collateral venous anastomosis
 - 3) incompetent valves of the internal spermatic vein

What are the effects of a varicocele on testicular function?

- associated with an adverse effect on spermatogenesis in a subset of men
- toxic effect may be manifested as;
 - a) **testicular growth failure**
 - b) **semen abN'ity,**
 - c) **Leydig cell dysfunction**
 - d) **histologic changes** } **tubular thickening, interstitial fibrosis, decreased spermatogenesis, maturation arrest**
- unilateral varicocele may result in bilateral changes
 - worse in ipsilateral testis

What are the possible theories to explain the effects of varicoceles on testicular function?

- 1) reflux of adrenal metabolites
- 2) hyperthermia
- 3) hypoxia
- 4) local testicular hormonal imbalance
 - Leydig cell dysfunction due to decreased intratesticular testosterone levels
 - serum FSH/LH/testosterone normal
- 5) intratesticular hyperperfusion injury

What is the classification system for varicoceles?

- Grade 1 → palpable only with Valsalva
- Grade 2 → palpable with patient standing
- Grade 3 → visible and palpable with patient standing

What are the important points to consider when assessing a child with a varicocele?

- 1) testicular volume } main criteria used for management decisions
 } semen analysis and hormone stimulation testing not practical in kids
 → N size differential can be up to ~20% of volume or 2mL
- 2) testicular consistency
- 3) contralateral side
→ no role in looking for subclinical varicoceles with imaging

What are the indications to treat a pediatric varicocele?

- ipsilateral testis >20% or >2mL smaller than contralateral testis
- painful varicocele

What are the management options for varicoceles in kids?

→ catch-up growth seen after ablation

- 1) retroperitoneal ligation of internal spermatic vein
 - short OR time & fast recovery
 - via small muscle-splitting incision made at level of ASIS
 - mass ligation of spermatic vessels VS artery-sparing
- 2) laparoscopic varicocele ligation
 - no significant benefit } slightly shorter hospital stay but significantly higher cost
- 3) inguinal ligation
 - can preserve testicular artery with use of microscope and Doppler
- 4) subinguinal ligation
 - may be more difficult to ligate all veins and also to identify testicular artery
 - faster than inguinal ligation (inguinal canal not opened)
- 5) transvenous embolization
 - slightly higher vascular complications than adults due to smaller caliber vessels
 - long GA anesthetic required

What are the potential complications of varicocelectomy?

- hydrocele formation } most common after RP ligation & least likely after embolization
- recurrence of varicocele } less likely with use of microscope and with RP mass ligation
- testicular atrophy
- ilioinguinal nerve injury
- vas deferens injury
- infection
- bleeding/hematoma

CONGENITAL ANOMALIES OF THE VAS, SEMINAL VESICALS and EPIDIDYMIS

What is the significance of agenesis of the vas?

- may occur unilaterally or bilaterally
 - bilateral congenital absence of vas deferens (CBAVD) is associated with CF
 - CBAVD occurs in 65-95% of men with CF
- may be associated with unilateral or bilateral hypoplasia or absence of other portions of wolffian duct remnants
 - with unilateral agenesis of vas } 75% have only 1 head of epididymis
 - } 20% have no ipsilateral epididymis
 - } 86% have ipsilateral agenesis of SV
 - } 20% have bilateral SV agenesis
 - with CBAVD } 68% have absence of portion of epididymis bilaterally
 - } 45% have absence of SV
- **men with vasal agenesis should have renal U/S**
 - 14-21% renal anomalies in men with CBAVD
 - 25-80% renal anomalies in men with unilateral vasal agenesis
 - **ipsilateral renal agenesis is most common finding**

What is the significance of a persisting mesonephric duct?

- **ectopic ureter draining into vas**
 - ipsilateral kidney is poorly functioning } renal dysplasia in many cases
 - often present with UTI or epididymitis
 - persisting mesonephric duct syndrome is also associated with imperforate anus
- Rx → depends mainly on function of unilateral kidney

What is the significance of epididymal cysts (spermatoceles)?

- usually asymptomatic
 - increased incidence in VHL syndrome and in offspring of women treated with DES
 - usually in head of epididymis
- Rx → surgical excision if increasing size or pain } observation for most cases

Chapter #128 – Sexual Differentiation

NORMAL SEXUAL DIFFERENTIATION

What are the 3 main steps in sexual differentiation (Jost)?

- 1) establishment of **chromosomal sex** at fertilization
- 2) development of undifferentiated **gonads into testes or ovaries**
- 3) subsequent **differentiation of internal ducts & external genitalia** based on endocrine function associated with the type of gonads present

Chromosomal sex

What is the significance of the Y chromosome in sex determination?

- presence of a Y chromosome results in the development of a male embryo, regardless of the number of X chromosomes
- contains the SRY gene, which is the testis-determining factor (TDF)
 - at one point, H-Y antigen and ZFY were thought to be the TDF
 - **SRY gene** is located on **short arm of Y chromosome (Yp)**
 - located adjacent to pseudoautosomal boundary

What is the role of the SRY gene found on the Y chromosome?

- SRY protein functions as a transcription factor
- contains SOX HMG-box sequence that acts as DNA binding site
- presence of SRY gene results in phenotypic male
 - 46, XX with SRY sequence becomes phenotypic male
 - 46, XY with mutation of SRY sequence becomes phenotypic female

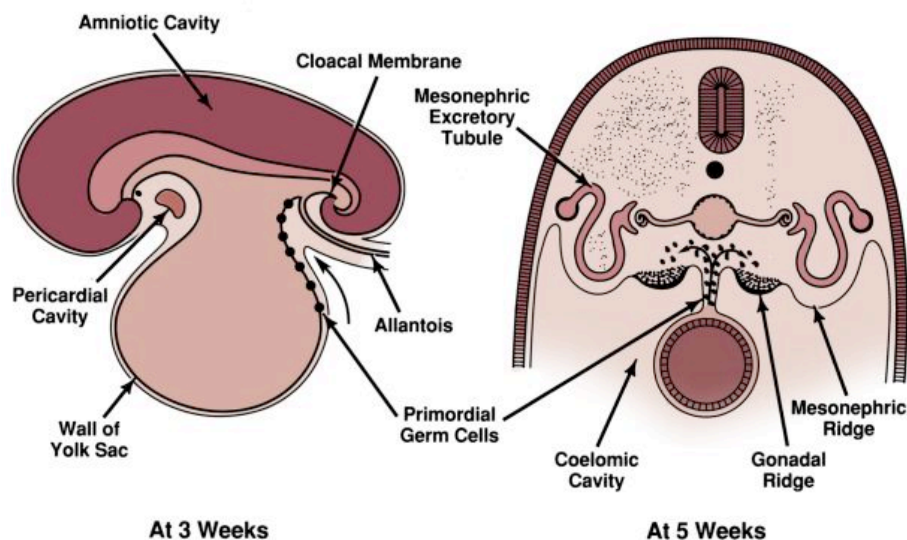
What other genes have been found to be involved in sex determination?

- WT1 } originally isolated as oncogene on chromosome 11 involved in Wilms' tumor
 - exerts its effects upstream of SRY
- SF1 } regulates enzymes involved in steroid production
 - regulator of mullerian-inhibiting substance (MIS)
- SOX9 } structurally similar to SRY gene
 - also a transcription factor involved in gonadal differentiation
- DAX1 } X chromosome gene involved in female sex differentiation
 - presence in 46, XY results in phenotypic female even if normal SRY gene
- WNT4 } found on chromosome 1p34 and acts as an anti-testis gene
 - presence in 46, XY results in phenotypic female

Gonadal differentiation

When does gonadal differentiation occur?

- first 6 wks } gonadal ridge, germ cells, internal ducts & external genitalia are all bipotential in both 46, XY and 46, XX embryos
 - primordial germ cells form by 3rd week
 - by 5th week germ cells migrate to medial ventral aspect of the gonadal ridge
- by 6-8 weeks } in the presence of SRY, indifferent gonad begins testicular organogenesis
 - gonadal ridges = testes
 - germ cells = spermatogonia
 - Sertoli cell differentiation by 7-8 weeks in response to SRY protein
 - Sertoli cells produce MIS
 - differentiation of Leydig cells occurs by 8-9 weeks in response to SRY protein
 - Leydig cells produce testosterone
- } in the ABSENCE of SRY, indifferent gonad begins ovarian organogenesis
 - gonadal ridges = ovaries
 - germ cells = oogonia } maximum 20 million cells by 20 weeks
 - no genes direct development of ovaries directly
 - 2 copies of X chromosome necessary
 - dysgenetic ovaries seen in 45, XO



→ MIGRATION OF PRIMORDIAL GERM CELLS

What are the rate-limiting enzymes involved in fetal sex differentiation?

- males (testosterone) } **3β -hydroxysteroid dehydrogenase**
 - 50x higher in fetal testis than ovary
- females (estrogen) } **aromatase**
 - higher in fetal ovary

What is MIS?

- Mullerian-Inhibiting Substance
- 1 of 2 hormones necessary for male sexual differentiation } SRY and MIS
- **secreted by Sertoli cells by week 7-8 in response to SRY**
- part of TGF- β family
- **gene found on chromosome 19**
 - lack of MIS in XY male DOES NOT mean no testes } means will have internal female organs

What is the role of Testosterone in sex differentiation?

- **produced by Leydig cells starting at ~9 weeks**
- becomes dependent on placental hCG secretion
- later in gestation, with declining hCG, testosterone synthesis is controlled by pituitary LH
- **testosterone is essential for virilization of Wolffian duct structures, the UG sinus, and the genital tubercle } enters tissue by passive diffusion**
- a local source of T is more important than peripheral T in circulation
- T is converted to DHT by intracellular 5α -reductase in some cells
- AR binds DHT with greater affinity and stability than T
 - **therefore, DHT is the active androgen in tissues such as the UG sinus, prostate, and external genitalia (all have 5α -reductase)**
 - **abN or deficient 5α -reductase enzyme results in abnormal virilization**
- T and DHT bind to androgen receptors (AR) that result in changes in nucleus
 - **AIS results in normal testosterone levels but no virilization**
 - **exogenous androgen produces virilization in females because AR is present within female tissues**

What is the role of estrogens in sex differentiation?

- **production detectable at 8 weeks**
- estrogen is NOT essential for feminization but can interfere with male differentiation
 - estrogen can block the effect of MIS
 - maternal prenatal estrogen exposure can lead to male reproductive tract abN'ities

When are the endocrine products of male gonadal differentiation seen?

- SRY protein } earliest
- MIS } made by Sertoli cells at 7-8 wks
- Testosterone } made by Leydig cells at 9 wks

Phenotypic Sexual Differentiation

How does phenotypic sexual differentiation occur in males?

- fetus is undifferentiated at 7wks gestation
- Sertoli cells produce MIS by week 7-8
 - MIS acts locally and unilaterally to suppress mullerian ducts
 - degeneration of mullerian ducts occurs by 10 weeks
- Leydig cells produce testosterone by week 8-9
 - local T permits local development of wolffian ducts
 - systemic T with conversion to DHT allows masculinization of external genitalia
 - external genitalia formed by 12-13 weeks

What male structures derive from wolffian ducts?

- efferent ducts
- epididymis
- appendix epididymis (remnant)
- vas deferens
- SVs
- ejaculatory ducts
- paradidymis (remnant)
- CZ if prostate
- ureter
- renal pelvis/calyces
- distal collecting duct

What are male mullerian duct remnants?

- prostatic utricle
- appendix testis
- verumontanum

What are the origins of the male external genitalia?

- glans penis → genital tubercle
- shaft of penis → urethral/genital folds
- scrotum → genital swellings

How does phenotypic sexual differentiation occur in females?

- T is not secreted by ovaries
 - lack of T results in regression of wolffian ducts
 - lack of T results in feminization of external genitalia
- MIS is not produced by ovaries
 - mullerian ducts are maintained and develop
- estrogen not essential for feminization (**mainly a lack of T and MIS**)

What female structures derive from mullerian ducts? What are female wolffian duct remnants?

- fallopian tubes
- uterus
- uterine cervix
- proximal 2/3 of vagina
- Gartner's duct
- epoophoron, paraoophoron
(organ of Rosenmuller)

What are the origins of the female external genitalia?

- clitoris → genital tubercle
- labia minora → urethral/genital folds
- labia majora → genital swellings

Homologues

Male	Female
Prostate gland	Skene's gland
Prostatic urethra	Entire urethra
Prostatic Utricle	Vagina, uterus
Vas, Ejaculatory duct	Gartner's duct
Cowper's glands	Bartholin's glands
Glans	Clitoris
Penile urethra	Labia minora
Scrotum	Labia majora
epididymis	epoophoron, paraoophoron
gubernaculum	Round ligament

Psychosexual differentiation

What are the 4 aspects of sexually dimorphic behaviour?

- 1) gender identity } identification of self as male or female
 - multifactorial and not just chromosomes or prenatal endocrine milieu
- 2) gender role } aspects of behaviour specific to males and females
 - likely related to prenatal endocrine influences
- 3) gender orientation } choice of sexual partner (hetero, homo, bi)
- 4) cognitive differences

ABNORMAL SEXUAL DIFFERENTIATION

What are the 4 main classifications of abN sexual differentiation (CHART)?

→ based on Grumbach & Conte classification (1998)

→ **new terminology in red } Disorders of Sex Development (DSD)**

1) disorders of GONADAL DIFFERENTIATION } Sex chromosomal DSD

- a) seminiferous tubule dysgenesis
 - Klinefelter's syndrome (47, XXY)
 - 46, XX male
- b) syndromes of gonadal dysgenesis
 - Turner's syndrome
 - pure/complete gonadal dysgenesis (46,XX and 46,XY)
 - mixed gonadal dysgenesis (MGD)
 - partial gonadal dysgenesis (dysgenetic male pseudohermaphroditism)
 - bilateral vanishing testis/testicular regression syndrome
- c) true hermaphroditism (**Ovotestis DSD**)

2) MASCULINIZED FEMALE (female pseudohermaphroditism) } **46,XX DSD**

→ **ovaries + partially masculinized phenotype + ambiguous genitalia**

- a) CAH } 21-hydroxylase, 11 β -hydroxylase, 3 β -hydroxysteroid dehydrogenase deficiencies
- b) maternal androgens
- c) maternal ovarian or adrenal tumour (androgen secreting)

3) UNDERMASCULINIZED MALE (male pseudohermaphroditism) } **46,XY DSD**

→ **testes + incomplete masculinization of genital ducts and/or external genitalia**

- a) Leydig cell agenesis, unresponsiveness
- b) disorders of testosterone biosynthesis
 - variants of CAH affecting corticosteroid & testosterone synthesis
 - StAR deficiency (congenital lipoid adrenal hyperplasia)
 - 3 β -hydroxysteroid dehydrogenase deficiency
 - 17 α -hydroxylase deficiency
 - 17,20-lyase deficiency
 - 17 β -hydroxysteroid oxidoreductase deficiency
- c) disorders of androgen-dependent target tissue
 - AR and post-receptor defects
 - complete testicular feminization (complete AIS)
 - partial androgen resistance (partial AIS)
 - androgen resistance in infertile men
- d) disorders of testosterone metabolism by peripheral tissues
 - 5 α -reductase deficiency
- e) disorders of synthesis, secretion, or response to MIS
 - persistent mullerian duct syndrome

4) UNCLASSIFIED forms

- a) males } micropenis
- b) females } Mayer-Rokitansky-Kuster-Hauser syndrome

What is the most common karyotype in kids with DSD/intersex disorders?

→ **45,XO/46,XY mosaicism** } most have N testes & look M

→ degree of masculinization depends on amount of testicular tissue present in child

What are the disorders of gonadal differentiation?

- | Disorder | Karyotype | Gonads | Internal Genitalia | External Genitalia | Other |
|----------------------------|---------------------------|----------------------------------|--|--------------------|--|
| Klinefelter's | 47, XXY | Small, firm testes | N male | N male | risk of breast, testis tumours |
| 46, XX maleness | 46, XX (80% SRY +ve) | Small testes | N male | N male | risk of breast, testis tumours |
| Turner's | 45, XO (most common) | streak gonad | N female | N female | gonadectomy if Y material; renal anomalies |
| Pure gonadal dysgenesis | 46, XX | bilateral streak | N female | N female | no Y material so no need for gonadectomy |
| | 46, XY | bilateral streak | N female | N female | removal of both gonads d.t. risk of GCTs |
| MGD | 45,XO/46,XY (most common) | Dysgenetic testis + streak gonad | Female on streak/male on testis | Ambiguous (mostly) | risk of GCTs & Wilms' tumour |
| Partial gonadal dysgenesis | 45,XO/46,XY (most common) | B/L dysgenetic testis | variable (depends on ability of dysgenetic testis to secrete T & MIS – 2/3 F) | | Risk of GCTs |
| Bilateral vanishing testis | 46, XY | absent | Variable (depends on when testis vanished)
Never Mullerian structures, variable Wolffian structures | | |
| True Hermaphrodite | 46,XX (most common) | 1 or 2 ovotestes (67%) | Related to ipsilateral gonad | ambiguous | Risk of GCTs |

What is Klinefelter's syndrome?

- 1 in 1000 live births } **most common major abNity of sexual differentiation**
 - 1) karyotype
 - **47,XXY most common** } due to non-disjunction during meiosis
 - can also see 48,XXYY and 49,XXXYY
 - mosaic form has milder features (46,XY/47,XXY)
 - 2) gonads
 - testicles N during childhood but during adolescence become **small, firm atrophic testes**
 - eunuchoid
 - seminiferous tubules degenerate & are replaced by hyaline } Leydig cell hyperplasia
 } **tubulosclerosis on Bx**
 - **azoospermia**
 - presence of sperm = 46,XY/47,XXY mosaicism
 - 3) internal genitalia & 4) external genitalia
 - **N male**
 - 5) other features
 - hypogonadotropic hypogonadism } high LH/FSH + low-normal T levels
 - elevated estrogen & estradiol/T ratio
 - **gynecomastia** } **8x higher risk of breast Ca**
 - decreased androgen production prevents N secondary sexual development
 - poor muscle development, female fat distribution, sparse facial hair, female-pattern pubic hair, usually tall stature (long legs)
 - **higher risk of extragonadal GCTs, Leydig cell tumours, Sertoli cell tumours**
 - mildly impaired IQ
 - osteoporosis
- Rx → careful androgen supplementation for libido
 → reduction mammoplasty PRN
 → scrotal & breast surveillance for testis & breast tumours
 → ICSI for infertility

What is 46, XX maleness?

- 1 in 20,000 } may be related to Klinefelter's
 - 1) karyotype
 - **46,XX most common** } 80% are SRY +ve
 - **translocation of Y material to X chromosome most likely**
 - may also be due to sex reversal or undetected mosaicism with Y material
 - 2) gonads
 - **small testes** } seminiferous tubules degenerate & are replaced by hyaline
 - **azoospermia**
 - infertility in all
 - 3) internal genitalia
 - **N male**
 - 4) external genitalia
 - **N male in most** } **10% have hypospadias**
 - 5) other features
 - usually have some features of Klinefelter's
 - **except they are usually shorter**
 - hypergonadotropic hypogonadism } high LH/FSH + low-normal T levels
 - elevated estrogen and estradiol/T ratio
 - **gynecomastia** } **higher risk of breast Ca**
 - **higher risk of extragonadal GCTs, Leydig cell tumours, Sertoli cell tumours**
- Rx → selected androgen supplementation
- reduction mammoplasty PRN
 - scrotal & breast surveillance for testis & breast tumours

What is Turner's syndrome?

- syndrome due to presence of only 1 normal X chromosome } error in mitosis
- 1 in 2500 live births
- common cause of primary amenorrhea } often Dx'd because puberty never occurs
→ spontaneous puberty occurs in ~30%

1) karyotype

- 45,XO (most common – 50%)
- 46,XX (isochromosome X – 10-20%)
- mosaicism (30-40%) } most common is 45,XO/46,XX
 - if Y material present, at increased risk of masculinization & gonadoblastoma

2) gonads

- **streak gonads** } no oocytes present
 } 2-5% have normal gonads
 → infertility in all

3) internal genitalia & 4) external genitalia

- N female

5) other features

- **somatic features** } - broad chest - short 4th metacarpal bone
- (BLLAC SNNNS) - bicuspid aortic valve - hypoplastic nails
- low-set ears - nipples are widespread
- lymphedema at birth - pigmented nevi
- aortic coarctation - webbed neck
- cubitus valgus - **short stature**
- **renal anomalies in 30-60%** } multiple renal arteries (most common), horseshoe, URA
- hypergonadotropic hypogonadism } high LH/FSH + low estrogen & T levels

Rx → must r/o occult Y material using FISH or PCR } 7-30% risk of gonadoblastoma

→ prophylactic removal of streak gonads in Y mosaic Turner's by age 6

- not req'd if no Y chromosome

→ U/S screening to r/o renal & cardiac anomalies

→ exogenous hormones for height & puberty } hGH, estrogens, etc

→ management of glucose intolerance & osteoporosis

→ ART for pregnancy possible } higher rates of miscarriage, stillbirth, congenital malformations

What prenatal U/S findings are suggestive of Turner's syndrome?

- ↑'d nuchal translucency
- lymphedema
- cystic hygroma (neck mass)
- coarctation of aorta
- renal anomalies

What renal anomalies are associated with Turner's syndrome?

→ found in 30-60% of all Turner's patients } mainly in classic 45, XO type

- **multiple renal arteries found in 90% of Turner's patient**
- duplication or URA (20%)
- malrotation (15%)
- horseshoe kidney (10%)

What is 46,XX pure gonadal dysgenesis?

- 1) karyotype
 - **46,XX**
 - 2) gonads
 - **bilateral streak gonads** (no oocytes present) } 2-5% have normal gonads
→ infertility in all
 - 3) internal genitalia & 4) external genitalia
 - **N female**
 - 5) other features
 - related to Turner's syndrome but NO SOMATIC FEATURES } normal height
 - hypogonadotropic hypogonadism } high LH/FSH + low estrogen & T levels
- Rx → cyclic hormone replacement (estrogen + progesterone)
→ normal growth & no Y material present } **NO NEED for hCG nor gonadectomy**

What is 46,XY pure gonadal dysgenesis?

- usually presents in teens with delayed puberty } amenorrhea, lack of breast development
- 1) karyotype
 - **46,XY** } due to abN SRY gene or abN'ty in gene related to SRY protein function
 - 2) gonads
 - **bilateral streak gonads** (no oocytes present)
 - 3) internal genitalia & 4) external genitalia
 - **N female**
 - 5) other features
 - hypogonadotropic hypogonadism } high LH/FSH + low estrogen & T levels
 - **significant risk of GCTs** (30% risk by age 30) } gonadoblastoma most common (bilateral)
} can also get embryonal, choriocarcinoma
- Rx → removal of both streak gonads
→ cyclic hormone replacement (estrogen + progesterone)

What is mixed gonadal dysgenesis (MGD)?

- **2nd most common cause of ambiguous genitalia (after CAH)**
- 1) karyotype
 - **45,XO/46,XY mosaicism most common karyotype** } anaphase lag during mitosis
→ can also have 46,XY karyotype
 - 2) gonads
 - **dysgenetic testis + streak gonad** } testis is usually UDT
→ infertility in all (no germinal elements in testis)
 - 3) internal genitalia
 - **Mullerian structures on side of streak** } uterus, vagina, fallopian tubes present in most
 - **Wolffian structures on side of testis**
 - 4) external genitalia
 - variable } **ambiguous genitalia (majority)**
→ phallic enlargement, UG sinus + labioscrotal fusion, UDT
→ can also get phenotypic F w/ Turner's (25%) or N-appearing M (rare)
 - 5) other features
 - can have Turner's like somatic features } short stature variable
 - **↑'d risk of GCTs (15-20%)** } **gonadoblastoma most common**
} higher risk of GCTs in dysgenetic testis (cf streak gonad)
 - ↑'d risk for **Wilms' tumour**
 - syndromes assoc'd w/ MGD } **Denys-Drash syndrome, Frasier syndrome**
- Rx → gender assignment } based on potential for N function of external genitalia & gonads
→ **2/3 raised as females**
→ appropriate gonadectomy based on assigned gender } in M, orchiectomy + hormones
VS orchidopexy + surveillance
} in F, remove streak & dysgenetic testis
→ hGH if short stature & screen for Wilms' tumour

***** NB }} >90% of ALL INFANTS with 45,XO/46,XY mosaicism on karyotyping have N appearing male genitalia + N bilateral testes *****

What is partial gonadal dysgenesis?

- aka dysgenetic male pseudohermaphroditism
 - closely related to MGD
 - 1) karyotype
 - **45,XO/46,XY mosaicism most common karyotype** } anaphase lag during mitosis
→ can also have 46,XY karyotype
 - 2) gonads
 - **bilateral dysgenetic testis** } hypoplastic seminiferous tubules (resembles streak gonad)
 - 3) internal genitalia
 - **variable degree of persistence of mullerian structures** } depends on MIS secretion by dysgenetic testes
 - 4) external genitalia
 - **variable degree of external genital abnormality** } depends on ability of dysgenetic gonads to make testosterone
 - 5) other features
 - **↑'d risk of gonadal tumours** } gonadoblastoma or GCTs
 - **↑'d risk of Denys-Drash syndrome**
- Rx → gender assignment } based on potential for N fxn of external genitalia & gonads
→ **2/3 raised as females**
→ appropriate gonadectomy based on assigned gender } in M, orchiectomy + hormones
VS orchidopexy + surveillance
} in F, removal of both dysgenetic testes

What is bilateral vanishing testes syndrome?

- aka embryonic testicular regression syndrome
 - causes of testicular regression include **genetic mutation, teratogen, or bilateral torsion**
 - 1) karyotype
 - **46,XY**
 - 2) gonads
 - **absent**
→ testes were present at some point during embryogenesis but “vanished”
→ M sexual differentiation took place @ some point } unlike 46,XY pure gonadal dysgenesis (bilateral streaks)
 - 3) internal genitalia
 - no internal genitalia (early loss) OR N wolffian structure (intermediate or late loss)
 - **no Mullerian structures (testis made MIS before “vanishing”)**
 - 4) external genitalia
 - **variable } depends on timing of loss of testicular tissue**
→ complete F with no internal genitalia } early loss (“testicular regression syndrome”)
→ ambiguous genitalia } intermediate loss
→ Wolffian structures + M phenotype w/ micropenis + empty scrotum } late loss (“vanishing testis syndrome”)
 - 5) other features
 - hypogonadotropic hypogonadism } high LH/FSH + low estrogen & T levels
- Rx → based on phenotypic position in spectrum of disorder
→ ambiguous genitalia } gender assignment
→ F } estrogen replacement at puberty, vaginoplasty
→ M } androgen replacement at puberty, testicular prostheses

What is true hermaphroditism?

- **aka Ovotestis DSD**
- **testicular tissue w/ good seminiferous tubules + ovarian tissue w/ primordial follicles**

1) karyotype

- **most commonly 46,XX (60%)**
 - can also get 46,XX/46,XY or 46,XX/46XXY mosaicism (33%) and 46,XY (7%)

2) gonads

- **most common is 1 or 2 ovotestes (67%)** } can have 1 ovary and 1 testis
 - ovary more common on L side
 - testes & ovotestes more common on R
- 60% of palpable gonads in inguinal canal or labioscrotal folds are ovotestes
- **with ovotestes, ovarian portion is often N while testicular portion is dysgenetic**
 - male infertility

3) internal genitalia

- **differentiation of internal ducts related to ipsilateral gonadal function**
 - ovary always assoc'd with fallopian tubes
 - testis always assoc'd with vas deferens
 - **ovotestis usually has fallopian tube (67%)**
 - **most also have uterus and UG sinus**

4) external genitalia

- **usually have ambiguous genitalia but slightly masculinized** } **75% raised as male**
 - raised as M } 80% have hypospadias + chordee
 - raised as F } almost all have UG sinus, most have uterus & 2/3 have clitoromegaly

5) other features

- can present with cyclic hematuria
- increased risk of gonadal tumours, especially if 46,XY

Rx → gender assignment } most important aspect (**75% raised as males**)

} based on potential for N fxn of external genitalia, internal ducts & gonads

→ if female } removal of all testicular & wolffian tissue

→ if T increases with hCG stim test post-op, then still some testicular tissue

} cyclic hormonal replacement

→ may not be needed if normal ovarian function

} fertility is possible if raised as female with appropriate ductal structures

} surveillance for potential gonadal tumours advised

→ if male } removal of all ovarian & mullerian tissue

- } consider gonadectomy + androgen replacement

→ higher risk of GCTs

→ fertility unlikely anyways

MASCULINIZED FEMALE (46,XX DSD)

What is a masculinized female?

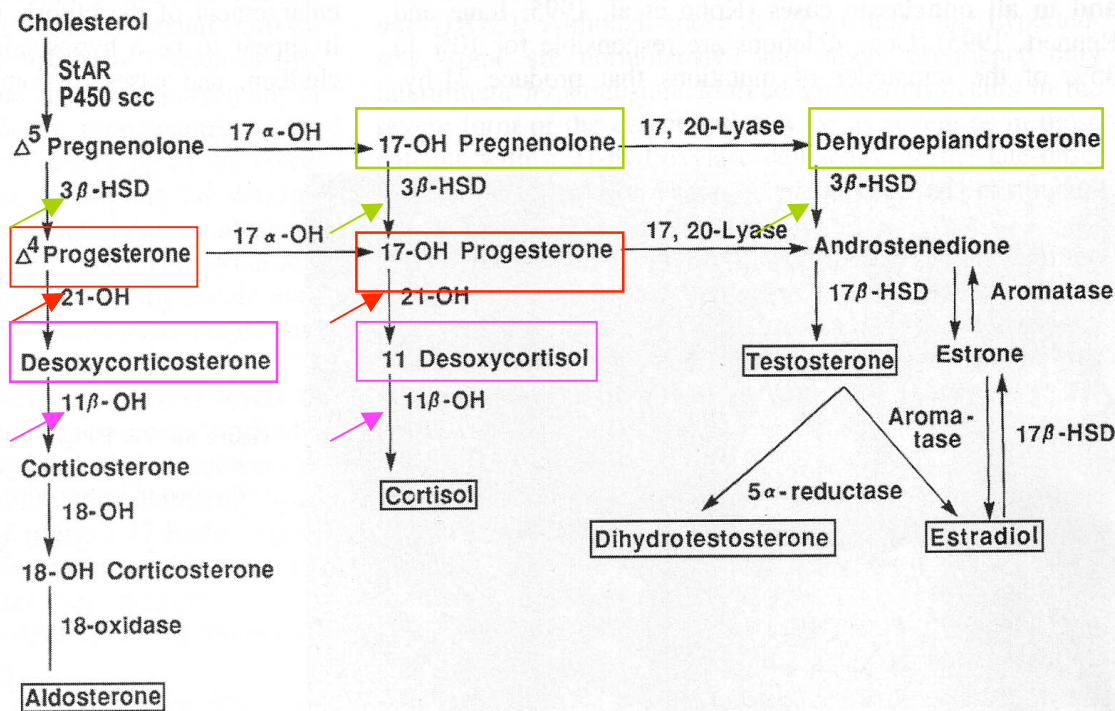
- aka female pseudohermaphroditism } disorder of phenotypic sexual development
- **46,XX + ovaries + N female internal genitalia + ambiguous genitalia** (partial masculinization)
 - clitoromegaly, varying degrees of labial fusion, common UG sinus
 - mullerian structures usually N
 - virilization more severe with CAH due to 21-hydroxylase deficiency
- **3 main causes of 46,XX DSD**
 - a) **CAH** } 21-hydroxylase, 11 β -hydroxylase, 3 β -hydroxysteroid dehydrogenase deficiencies
 - **CAH is most common cause of ambiguous genitalia in newborn** (MGD 2ND)
 - b) maternal androgens (rare)
 - c) maternal ovarian or adrenal tumour (rare) } androgen secreting

What is CAH?

- classic inborn error of metabolism involving cortisol synthesis } occurs in ~1 in 10,000
- defect in any 1 of 5 enzymes involved in cortisol biosynthesis pathway
 - a) cholesterol side chain cleavage enzyme
 - b) 3 β -hydroxysteroid dehydrogenase (least common)
 - c) 17 α -hydroxylase
 - d) **21-hydroxylase** } **most common deficiency (95%)** → type I and type II CAH
 - e) **11 β -hydroxylase** } **second most common** → type III CAH
- impaired hydrocortisone synthesis results in compensatory increase in ACTH
 - then get increased adrenal testosterone

What are the 3 forms of CAH due to 21-hydroxylase deficiency?

- abn CYP21 gene on chromosome 6p21 (HLA-linked) } **AR inheritance pattern**
- 1) classic forms
 - a) salt wasters (75%) → virilization + aldosterone deficiency
 - b) simple virilizers (25%) → virilization only
- 2) nonclassic (rare) } no virilization & no salt wasting



→ STEROID BIOSYNTHESIS } MINERALOCORTICOID, GLUCOCORTICOID, SEX STEROID (GFR = A, C, T)

What is the usually presentation of CAH secondary to 21-hydroxylase deficiency?

- ↑'d plasma 17-OH-progesterone & progesterone
- ↑'d urinary 17-ketosteroids & pregnanetriol
- pelvic U/S showing presence of mullerian tissue helps confirm Dx
- **all F present with ambiguous genitalia**
 - enlarged clitoris
 - UG sinus
 - varying degrees of labial fusion } virilization more severe in salt-wasting forms
- **all males have N genitalia at birth**
- PRADER classification of various degrees of masculinization of external genitalia of the F with CAH is often applied to all DSDs
- 1) **SALT-WASTING variant most common (75%)**
 - failure to regain birth weight
 - progressive weight loss
 - dehydration
 - adrenal crisis can occur
 - **vomiting (can be so severe that it's mistaken for pyloric stenosis)**
 - **hyperK + hypoNa** (no aldosterone)
 - progression of masculinization of unRx'd female (acne, deeper voice, early pubic hair, etc)
- 2) **SIMPLE VIRILIZING variant (25%)**
 - progression of masculinization of unRx'd female
 - males show signs of sexual & somatic precocity within first 2-3 yrs } "little Hercules"
 - testes remain N but get enlarged penis, scrotum, prostate, pubic hair, acne, & well developed muscles
 - develop infertility & short stature long-term
- 3) non-classic form (rare)
 - late-onset form that is variable in clinical severity & timing of onset
 - F presents with hirsutism, oligomenorrhea, male pattern baldness, PCO
 - M presents with oligospermia & subfertility
- Rx → glucocorticoids (lower doses needed for non-classic form of CAH) } females don't menstruate without Rx

What are the 2 forms of CAH due to 11β-hydroxylase deficiency?

- abN CYP11B1 gene on chromosome 6p21 (NOT HLA-linked)
- 1) classic form } can get severe virilization, almost as much as 21-hydroxylase deficiency
- 2) mild form } signs of androgen excess not seen until childhood or adolescence (later onset)

What is the usually presentation of CAH secondary to 11β-hydroxylase deficiency?

- ↑'d plasma 11-deoxycortisol & 11-deoxycorticosterone (DOC)
- ↑'d urinary 17-ketosteroids & 17-OH-corticoids
- HTN (common) } from elevated DOC (has some aldosterone activity)
- virilization
- Rx → same glucocorticoid treatment as 21-hydroxylase deficiency

How do you differentiate between the various forms of CAH?

- **21-hydroxylase deficiency** } ↑d serum plasma 17-OH-progesterone & progesterone (95%) } better than 24hr urine for 17-ketosteroids or pregnanetriol
- **11β-hydroxylase deficiency** } ↑d serum 11-deoxycortisol & 11-deoxycorticosterone (DOC) } increased urinary 17-ketosteroids or 17-hydroxycorticoids
- **3β-hydroxysteroid dehydrogenase deficiency** } ↑d serum 17-OH-pregnenolone & DHEA

What is the role of prenatal diagnosis of CAH?

- Dx can be made by measuring 17-OH-progesterone in amniotic fluid at 16-17 wks } very late
 - **Dx made by HLA genotyping or DNA analysis of genes in cells from CVS at 10-11 weeks**
- Rx → dexamethasone
- should start at 5-6 wks, before initial development of ext. genitalia } can't confirm Dx before Rx
- *** problem } virilization of male fetus not a concern \ 7/8 fetuses will be
- } AR inheritance so 3/4 female fetuses at risk are unaffected / Rx'd unnecessarily

What are the goals of therapy of CAH?

- 1) replace deficient hormone (glucocorticoid +/- mineralocorticoid)
- 2) suppress adrenal androgens & clinical virilization
- 3) ↓ rapid somatic growth and osseous advance
- 4) permit N gonadal development
- 5) correct salt-water loss or HTN

What is the management for CAH?

- 1) Investigations (“FUUKED Large, Then Gone After 17”)
 - **Electrolytes, FSH, LH, Testosterone, DHT, Anti-Mullerian hormone (MIS)**
 - **plasma progesterone, 17-OH-progesterone**, 11-desoxycortisol, 11-desoxycorticosterone (DOC), 17-OH-pregnenolone & DHEA
 - **Urine 17-ketosteroids**, pregnanetriol & 17-hydroxycorticoids
 - **Karyotype**
 - **pelvic Ultrasound** } to demonstrate mullerian tissues (confirms dx)
 - **Genitogram of UG sinus**
- 2) Management
 - control electrolytes and BP
 - steroid replacement } hydrocortisone initially
 - } fludrocortisone 0.05-2.5mg OD as maintenance (if salt-waster)
 - pts instructed to triple hydrocortisone during stress (surgery, infection)
 - salt } add to diet
 - genitoplasty } **usually F gender assignment**
 - feminizing genitoplasty at 3-6 months
 - clitoral reduction + vaginoplasty
 - consider “prophylactic” adrenalectomy
 - used experimentally in selected pts } more difficult to maintain adrenal suppression than to prevent adrenal crises
 - usually in severe salt-wasters & extremely virilized females where high cortisol supplementation has resulted in significant hypercortisolism (poor growth, obesity, infertility)
- 3) Prevention (controversial)
 - ?prenatal treatment w/ dexamethasone to prevent virilization
- 4) Surveillance
 - monitor plasma 17-OH-progesterone
 - follow lytes, BP

What maternal agents have been associated with female virilization?

- danazol } endometriosis Rx
- progestational agents } to prevent threatened abortion

What maternal androgen producing tumours have been associated with female virilization?

- ovarian or adrenal tumours } arrhenoblastoma, hilar cell tumour, lipoid cell tumour, ovarian stromal cell tumour, luteoma of pregnancy, Krukenberg's tumour, adrenocortical carcinoma, etc

UNDERMASCULINIZED MALE (46,XY DSD)

What is an undermasculinized male?

- aka male pseudohermaphroditism or 46,XY DSD
- **46,XY + testes + variable masculinized internal organs + ambiguous genitalia**
→ incomplete masculinization of genital ducts and/or external genitalia
- **5 main causes**
 - a) Leydig cell agenesis, unresponsiveness (LH receptor abN'ity)
 - b) disorders of T biosynthesis
→ variants of CAH affecting corticosteroid & T synthesis
 - StAR deficiency
 - 3 β -hydroxysteroid dehydrogenase deficiency
 - 17 α -hydroxylase deficiency
 - 17,20-lyase deficiency
 - 17 β -hydroxysteroid oxidoreductase deficiency
 - c) disorders of androgen-dependent target tissue
→ **AR & post-receptor defects (most common cause of undervirilized male)**
 - complete testicular feminization (complete AIS)
 - partial androgen resistance (partial AIS)
 - androgen resistance in infertile men
 - d) disorders of testosterone metabolism by peripheral tissues
 - 5 α -reductase deficiency
 - e) disorders of synthesis, secretion, or response to MIS
 - persistent mullerian duct syndrome

Disorder	Karyotype	Gonads	Internal Genitalia	External Genitalia	Other
Leydig Cell aplasia	46,XY	testes	no mullerian structures	appears F	Can find testes in hernia
Disorders of T biosynthesis (5 CAH variants)	46,XY	testes	no mullerian structures	female or ambiguous	17 β -HSD can develop M pubertal changes 50% have hernias (can find testes); risk of testis Ca
complete AIS	46,XY	testes	no mullerian structures	appears F	
partial AIS	46, XY	testes	no mullerian structures	ambiguous	
5AR deficiency	46, XY	testes	wolffian structures	variable ambiguity	M pubertal changes
Persistent Mullerian Duct Syndrome	46,XY	testes	mullerian structures	N male	risk of testis Ca

What is Leydig cell aplasia?

- LH receptor abN'ity with AR inheritance
- **46,XY + testes + no mullerian structures + N-appearing F genitalia** (short vagina)
→ gonads found in labia majora or inguinal canal
- elevated LH and low T } absence of rise in T after hCG stimulation
- **N Sertoli cells but no Leydig cells** } DDx includes **complete AIS** & terminal defect in androgen synthesis
- often Dx'd due to absence of secondary sexual characteristics

What are the 5 disorders of T biosynthesis?

- **AR inheritance** for all 5 enzyme deficits
- **variants of CAH (incomplete or absent virilization)**
 - deficiency of StAR & 3 β -hydroxysteroid dehydrogenase also have cortisol & aldosterone defic.
 - these 2 enzymes are in testis & adrenal
- **46,XY + testes + no mullerian structures + female or ambiguous genitalia**
 - Wolffian structures are present or present but primitive
- 1) StAR (cholesterol side chain cleavage enzyme) deficiency } aka “congenital lipoid adrenal hyperplasia”
 - present early w/ severe cortisol & aldosterone deficiency } hypoNa, hyperK, met acidosis
 - see large, fat-rich adrenals on CT
 - Rx → glucocorticoids + mineralocorticoids + mostly assigned F gender (gonadectomy)
- 2) 3 β -hydroxysteroid dehydrogenase deficiency
 - present early w/ severe cortisol & aldosterone deficiency } hypoNa, hyperK, met acidosis
 - Rx → glucocorticoids + mineralocorticoids + mostly assigned F gender (gonadectomy)
- 3) 17 α -hydroxylase deficiency
 - **get excess aldosterone activity } hyperNa, HTN, hypoK**
 - Rx → glucocorticoids + gender assignment (male + T OR female + gonadectomy + estrogen)
- 4) 17,20-lyase deficiency
 - no defect in glucocorticoid or mineralocorticoid synthesis } N cortisol & ACTH secretion
 - Rx → genitoplasty + appropriate sex hormone replacement at puberty
- 5) 17 β -hydroxysteroid oxidoreductase deficiency
 - similar to 5AR deficiency
 - at birth, they have N female external genitalia + N testes + N wolffian structures
 - then **get N male pubertal Δ 's** } phallic growth + development of M 2° sexual characteristics
 - Rx → gender assignment based on timing of Dx (child or at puberty)
 - most are raised F if not Dx'd early } ?reassignment to M during puberty

What is complete androgen insensitivity syndrome (AIS)?

- aka testicular feminization (obsolete term)
- **46,XY + testes + absent mullerian structures + F-appearing external genitalia**
 - **vagina is short & blind-ending**
 - testes do secrete MIS but have incomplete or absent spermatogenesis
- **X-linked inheritance** } point mutation accounts for 90% of AIS
- Dx often made during w/u for primary amenorrhea or during herniorrhaphy (finding testis)
- **4 types of receptor defects** }
 - 1) decreased amount of N receptor
 - 2) no receptor binding
 - 3) abN receptor
 - 4) other “receptor-positive” forms (eg ↑'d dissociation of steroid-receptor complex)
- **50% have inguinal hernias** } but only 1-2% of apparent F + inguinal hernias have complete AIS
 - **vaginoscopy (confirm cervix) before hernia repair in F**
- at newborn age, get normal levels of T, DHT, and gonadotropins
- at puberty, increased gonadotropins lead to **increased T & estradiol**, resulting in feminization
- **2-5% risk of testis Ca (peri & post-puberty)** } **gonadoblastoma & seminoma**
- Rx → **Female gender assignment for ALL**
 - delayed gonadectomy } remove after puberty so estrogens from testis allow for F development
 - must r/o partial AIS, otherwise will get virilization at puberty
 - risk of testis tumour is low before puberty so safe
 - } **if palpable or assoc'd w/ hernia, may decide to remove early**
 - **orchietomy significantly decreases libido so NOW not removed as often**
 - cyclic hormone replacement (estrogen and progesterone)
 - progressive dilation of short vagina vs vaginoplasty

What is partial androgen resistance syndrome?

- aka Reifenstein's syndrome, Gilbert-Dreyfus syndrome, Lubs syndrome
- **46,XY + testes + absent Mullerian structures + ambiguous genitalia**
- classic phenotype = M with perineoscrotal hypospadias + UDT + rudimentary wolffian structures + gynecomastia + infertility
- X-linked inheritance
- 2 forms of receptor defects } 1) reduced # of N receptors
2) N receptor # but decreased binding affinity
- as newborn, get normal levels of T, DHT, and gonadotropins
- at puberty, increased gonadotropins lead to increased T & estradiol, resulting in feminization and phallus may enlarge slightly
- Rx → **gender assignment depends on degree of genital virilization**
 - female assignment } gonadectomy + genitoplasty + cyclic hormones at puberty
 - male assignment } orchidopexy + reduction of gynecomastia + genital reconstruction
 - may get some androgen imprinting of fetal brain

What is 5 α -reductase deficiency?

- mutation in type 2 5-AR enzyme (chromosome 2) } higher levels in prostate & external genitalia
- AR inheritance
- **46,XY + testes + N wolffian structures + variable ambiguous genitalia**
 - varies from marked ambiguity to penoscrotal hypospadias
 - usually get small phallus (looks like clitoromegaly) + UG sinus + labioscrotal fusion
 - short, blind-ending vagina
- **partial virilization occurs at puberty with increased gonadotropins**
 - increased muscle mass, increased penis size, etc but NO prostatic enlargement or alopecia
- get **elevated serum T levels but low DHT levels**
 - ratio of T/DHT increases after hCG stimulation test
- genital skin fibroblast cultures shows diminished to absent 5 α -reductase activity
- Rx → **Male gender assignment favored if Dx made early (testosterone imprinting)**
 - male } hypospadias repair + orchidopexy + consider exogenous DHT at puberty for penile growth
 - female } early gonadectomy (prevent virilization at puberty) + cyclic hormones + vaginoplasty/clitoral reduction

What is Persistent Mullerian Duct Syndrome?

- aka "hernia uteri inguinale"
- either defect in MIS gene (chromosome 19) or in MIS type 2 receptor (chromosome 12)
- commonly Dx'd after seeing mullerian tissue at time of inguinal hernia repair or orchidopexy
- **46,XY + testes + internal mullerian duct structures + N male external genitalia**
 - bilateral fallopian tubes, a uterus, and an upper vagina draining into a prostatic utricle
 - usually see unilateral or bilateral **UDT**
- normal T and gonadotropins
- 3 classic presentations:
 - 1) **bilateral intra-abdominal testes in position analogous to ovaries** } 60-70%
 - 2) one testis in hernia sac or scrotum + contralateral inguinal hernia } 20-30%
 - 3) both testes found in same hernia sac (transverse testicular ectopia) with fallopian tubes and uterus } 10%
- 30-50% of transverse testicular ectopia cases are associated with PMDS
- **↑'d risk of testis tumours } most commonly seminoma**
- Rx → all are phenotypic **males**
 - orchidopexy + surveillance for testis tumours
 - can leave mullerian structures (uterus & proximal vagina) in order to avoid injury to nearby vas deferens

UNCLASSIFIED FORMS OF ABNORMAL SEXUAL DIFFERENTIATION

List the unclassified forms of abN sexual differentiation.

- 1) males } micropenis
- 2) females } Mayer-Rokitansky-Kuster-Hause syndrome

Disorder	Karyotype	Gonads	Internal Genitalia	External Genitalia	Other
Mayer-Rokitansky-Kuster-Hauser	46,XX	ovaries	absence of uterus & vagina	N female	GU tract anomalies in 1/3

What is micropenis?

- **N formed penis that is <2.5 SDs below the mean (ie <1.9cm in newborn)**
- usually have N ratio of length to girth } may have severe hypoplasia of corpora cavernosa
- scrotum usually fused but small
- **testes usually small undescended**
- often associated with major chromosomal defects (eg Klinefelter's)
- **true micropenis results from a hormonal abN'ity AFTER 14wks gestation**
- **if earlier, would result in differentiation issues + hypospadias also**

What is Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome?

- congenital absence of uterus and vagina
- **46,XX + ovaries + absence of uterus & vagina but other mullerian structures N (tubes) + N female external genitalia + N secondary sex characteristics**
- normal ovaries, fallopian tubes } normal function
- can see atypical forms } asymmetrical uterine remnants +/- aplasia of one or both fallopian tubes
- usually presents with primary amenorrhea or dyspareunia
- **33% have upper GU tract anomalies** } URA, pelvic kidney, or horseshoe kidney
- more common in atypical form (70%)

Rx → female gender

→ creation of neovagina } for sexual function & drainage of menstrual fluid (if atypical form)

List disorders associated with unilateral renal agenesis. } } } "Frazier, overTurned Bus on DVP, Killed Many"

- Fraser's
- Turner's
- BOR syndrome
- DiGeorge
- VACTERL
- Poland's
- Kallman's
- MRKH

List DSD/Intersex disorders associated with future risk malignancy.

- 1) Klinefelter's } breast, testis (non-GCT), extra-gonadal GCTs
- 2) 46,XX maleness } breast, testis (non-GCT), extra-gonadal GCTs
- 3) Turner's with XY mosaicism } breast, testis (GCT)
- 4) 46,XY Pure gonadal dysgenesis } testis (GCT)
- 5) MGD } testis (GCT), Wilms'
- 6) Partial gonadal dysgenesis } testis (GCT), Wilms'
- 7) Ovotestis DSD with XY mosaicism } testis (GCT)
- 8) complete AIS } testis (GCT)
- 9) Persistent Mullerian duct syndrome } testis (GCT)

EVALUATION AND MANAGEMENT OF NEWBORN AMBIGUOUS GENITALIA

What is the acute management of a newborn with ambiguous genitalia?

- 1) don't assign gender right away } changing gender later on can be traumatic
→ after Dx is made, assign sex based on Dx, child's anatomy, and functional potential of genitalia and reproductive tract
→ mostly raised female
→ only few raised M } **Klinefelters, 46,XX maleness, Ovotestis DSD, 5AR deficiency & Persistent Mullerian Duct Syndrome**
- 2) multi-disciplinary consults
→ pediatric urologist + endocrinologist + intersex psychologist
- 3) r/o acute life-threatening medical conditions
→ CAH

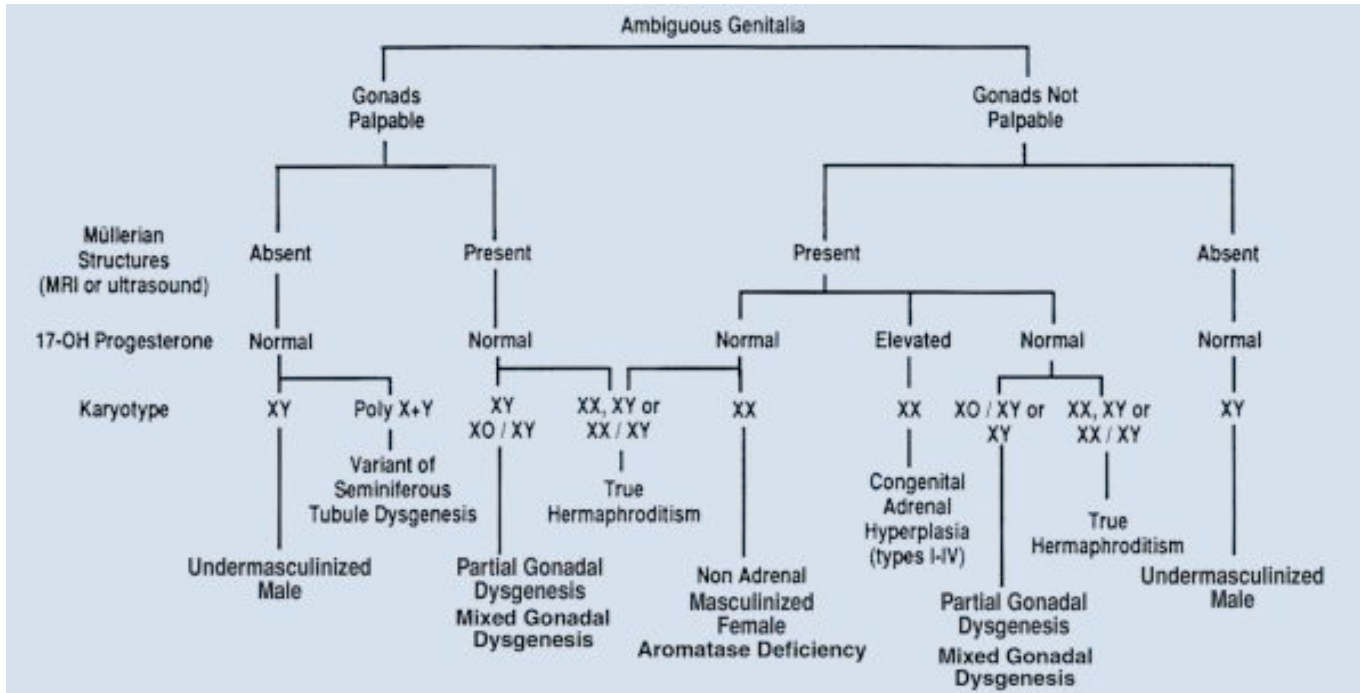
What is involved in the immediate work-up of ambiguous genitalia?

- 1) History
 - maternal use of meds (danazol, progesterone, steroids, BCP) during pregnancy
 - family history
 - familial infant death } may suggest CAH
 - infertility, amenorrhea, or hirsutism } may suggest familial patterns of intersex
 - antenatal U/S
- 2) Physical exam
 - **assess for signs of adrenal crisis (CAH)** } ++vomiting, wt loss, dehydration, etc
 - **bilateral impalpable testes OR unilateral impalpable testis + hypospadias should be considered intersex disorder (DSD) until proven otherwise**
→ very proximal hypospadias alone should be investigated (even if genitalia seems N)
 - general VSs
 - abdominal exam, lower back exam
 - **presence of 1 or 2 gonads** } ovaries don't descend, so likely testis
 - } rules out masculinization of female
→ CAH, maternal androgens
 - } may rarely be ovotestis that descended
→ true hermaphrodite (Ovotestis DSD)
 - examine external genitalia } penile size, stretched penile length, clitoral size, hypospadias, scrotum/labia, rectum
 - DRE } to rule out Mullerian structures (eg uterus felt in midline)
- 3) imaging
 - U/S } **identify any Mullerian structures** → r/o uterus
 - } identify & assess gonads & adrenals
 - genitogram } usually at time of surgery
- 4) **karyotype**
 - takes 2-3 days
 - FISH is faster than karyotyping } identifies X and Y chromosomes within few hrs
- 5) lab tests
 - serum **electrolytes** } **r/o salt-wasting CAH (hypoNa, hyperK)**
→ may be N } check renin
 - serum testosterone & DHT } to r/o 5 α -reductase deficiency (elevated ratio of T/DHT)
 - **serum 17-OH-progesterone** } r/o 21-hydroxylase CAH
→ not done until day 3-4 because stress of delivery can cause false elevations for first 1-2 days of life + maternal
 - serum gonadotropins (LH, FSH) + hCG stimulation test } if no palpable gonads
→ to r/o presence of testicular tissue
→ to distinguish impaired T synthesis (deficient response to hCG) from AIS (N response)
 - MIS
 - urinary 17-ketosteroids, pregnanetriol } r/o 21-hydroxylase CAH

What are the recommended initial tests for a child with ambiguous genitalia?

→ “if you have ambiguous genitalia at Sick Kids, you are “FUUKED Large, Then Gone After 17”

- FSH
- Ultrasound
- Urine tests (17-ketosteroids)
- Karyotype
- Electrolytes
- DHT
- LH
- Testosterone
- Genitography
- Anti-Mullerian hormone (MIS)
- 17-OH-progesterone (serum)



What is the next step in the work-up of ambiguous genitalia?

→ No Dx after P/E (gonads) + U/S (mullerian structures) + serum 17-OH-progesterone + karyotype + other bloodwork

- 1) diagnostic laparoscopy or laparotomy + gonadal Bx
 - should defer removal of any gonads or reproductive organs until final pathology report is available and gender has been assigned
- 2) endoscopic imaging
 - scope + genitography to assess UG sinus and ductal structures
 - define entry of urethra and vagina into sinus
 - look for cervix

What are the main issues to discuss after making the Dx before assigning gender?

- if Dx made pre-natally, must decide on management plan
- parental involvement is essential !!!

- 1) potential for **N sexual functioning and fertility**
- 2) **risk of gonadal malignancy**
- 3) **psychosocial** outcomes of gender assignment
 - no good quality, long term data

→ “Male And Females PMS”

- Malignancy risk
- Appearance
- Fertility potential
- Psychosocial outcomes
- Minimal medical procedures
- Sexual function

What are the more common gender assignments for kids with DSD/intersex disorders?

- masculinized female with 46,XX } usually female
- 46,XY with complete AIS } usually female
- 46,XY with 5 α -reductase deficiency } usually male

What are the Meyer-Bahlburg parameters of optimal gender assignment for ambiguous genitalia?

- 1) reproductive potential if attainable
- 2) good sexual function
- 3) minimal medical procedures
- 4) overall gender-appropriate appearance
- 5) stable gender identity
- 6) psychosocial well-being

What are the main points that must be addressed in the pt w/ abnormal sexual differentiation?

- chromosomes } karyotype
- testicular determinant factors
- gonads
- paracrine system: hormones + MIS
- internal duct structures } Mullerian vs. Wolffian
- endocrine system
- UG sinus
- external genitalia } phallus
- secondary sexual characteristics
- psychosexual identity
- fertility
- sexual function

What are the most common causes of ambiguous genitalia?

- overall, CAH is #1, MGD is #2
- ambiguous genitalia with 46,XX
 - **CAH (female)**
 - true hermaphrodite (ovotestis DSD)
- ambiguous genitalia with 46,XY
 - **impaired T synthesis disorder**
 - **partial AIS**
 - **5 α -reductase deficiency**
 - CAH (male)
 - MGD
 - Leydig cell hypoplasia/dysgenetic testes
- ambiguous genitalia with 45,XO/46,XY
 - **MGD**
 - Leydig cell hypoplasia/dysgenetic testes
- ambiguous genitalia with 46,XX/46,XY
 - true hermaphrodite (ovotestis DSD) } true hermaphrodite is most commonly 46,XX

Which DSD syndromes are associated with male pubertal development?

- usually raised female, then develop penis at puberty
- 1) 17 β -hydroxysteroid oxidoreductase deficiency (undermasculinized male with T synthesis problem)
- 2) 5 AR deficiency (undermasculinized male)
- 3) Partial AIS (undermasculinized male) } partial enlargement of phallus can be seen

Chapter #130 – Pediatric Oncology

What is the DDx of an abdominal mass in an infant?

- Kidney (65%)
 - **hydronephrosis (30%)** } UPJO, UVJO, ureterocele, etc) → **most common cause of abdo mass in neonate**
 - **MCDK** → **single most common entity**
 - Wilms' → **most common GU malignancy**
 - congenital mesoblastic nephroma → **most common solid renal mass in neonate**
 - PCKD
- Retroperitoneum (10%)
 - **neuroblastoma** → **most common solid abdo mass in child & most common malignancy**
 - sarcoma
 - teratoma
- Other
 - bladder (PUVs)
 - GI (cystic meconium ileus)
 - hepatobiliary (liver hemangioma)

NEUROBLASTOMA

What is a neuroblastoma?

- **neural crest tumour**
- arises from adrenal medulla or along sympathetic chain (neck, chest, pelvis or retroperitoneum)
 - **75% occur in retroperitoneum** } **50% adrenal** & 25% paravertebral ganglia
 - 4% occur in pelvis } from organ of Zuckerkandl
- can undergo spontaneous regression, differentiate into a benign tumour, or exhibit very malignant behaviour

What is the epidemiology of neuroblastoma?

- **most common extracranial solid tumour in kids** } 8-10% of all cancers in kids
 - 1 case per 100,000 live births
- **95% are Dx'd in kids before age 10yrs** } **most common malignant tumour of infants**
 - 75% Dx'd by 4yrs of age
 - median age at diagnosis is 21 months
 - **>50% of these kids have mets at Dx**
- familial cases exist
 - AD inheritance
 - earlier age at diagnosis (median age 9 months)
 - ≥20% have bilateral adrenal or multifocal primary tumours
 - risk in sibling or offspring is <6%
- may be diagnosed on prenatal U/S
 - clinically favorable course

What chromosomal abnormalities are associated with neuroblastoma?

- negative prognostic markers
 - **deletion of short arm of chromosome 1 (1p36)** } found in 70-80% of patients
 - **N-myc oncogene amplification** } found in 40% of advanced stage
 - } but only 5-10% of low-stage or stage 4S disease
- favorable prognostic marker
 - **aneuploidy of tumour DNA**

What is “in situ neuroblastoma”?

- small nodules of neuroblasts that are histologically indistinguishable from neuroblastoma
 - incidence is 40-45x greater than that of clinical neuroblastomas
- gives evidence of spontaneous regression

What is a ganglioneuroma?

- **histologically benign, fully differentiated counterpart of neuroblastoma**
- likely arises by maturation of pre-existing neuroblastoma or ganglioneuroblastoma
- usually diagnosed in older kids
- usually found in posterior mediastinum or retroperitoneum
- often grow to very large sizes before causing symptoms

What is the Shimada grading classification of neuroblastoma?

→ age-linked histopathologic classification

- 1) stroma-poor tumours
 - a) favorable histology
 - b) **unfavorable** histology } poor prognosis (<10% survival)
 } based on bad clinical features
 → age at Dx, degree of histologic maturation, & mitotic rate
- 2) stroma-rich tumours
 - a) **nodular** } **bad prognosis**
 - b) intermixed \ - high rate of survival
 - c) well differentiated / - resembles ganglioneuroblastomas or immature ganglioneuromas

What is the Joshi grading system of neuroblastoma?

- grade 1 } low mitotic rate (<10 mitotic figures/HPF) + calcifications
- grade 2 } low mitotic rate OR calcifications
- grade 3 } neither low mitotic rate NOR calcifications

How does neuroblastoma usually present?

→ 50-70% have mets at Dx } KIDS ARE SICK

- **abdominal pain**
- **abdo mass that CROSSES MIDLINE**
- “blueberry muffin” (subcutaneous nodules)
- cough or dyspnea (thoracic)
- bowel or bladder symptoms (extrinsic compression)
- neurologic deficits (direct extension into spinal canal)
- bone or joint pain (mets)
- periorbital ecchymosis (mets)
- **paraneoplastic syndromes**
 - release of catecholamines } paroxysmal HTN, palpitations, flushing, H/A
 } mimics pheochromocytoma
 - release of VIP } severe watery diarrhea & hypoK
 - acute myoclonic encephalopathy } myoclonus, multi-directional REMs (opsoclonus) & ataxia
 → interaction of Ab’s against neuroblastoma & N nerves
 } favorable outcome from cancer perspective but usually get developmental delay, etc
 Rx → ACTH (most effective), high-dose IVIG,
 cyclophosphamide
- fleshy on gross pathology } pink rosette (flower-like) on micro pathology

What is the work-up for a possible neuroblastoma?

- 1) Lab tests

- [illegible]

2) Imaging

- plain X-ray } calcified abdo or posterior mediastinal mass
- U/S
- CT } good information on local extent of tumour
- MRI } better than CT because can evaluate intraspinal tumour extension
- bone scan } to detect cortical bone mets (usually long bones or skull)
- MIBG scan } can show both primary tumour & mets

What is the role of screening for neuroblastoma?

→ mainly done in Japan

- **neuroblastoma Dx'd on screening test has more favorable outcome } >97% survival**
- less likely to have N-myc amplification & more likely to be aneuploid } favorable features
- **HOWEVER, # of older kids with advanced-stage disease at Dx has not decreased**
 - suggests that aggressive advanced-stage neuroblastomas DON'T come from low-risk tumours (ie are de novo rather than progression)
- **NO ROLE FOR SCREENING, as they detect lesions that likely would regress in future**

What is the staging system used for neuroblastoma (CHART)?

→ International Neuroblastoma Staging System (INSS)

→ based on clinical, radiographic, & surgical evaluation

→ determines intensity of CHEMO and RADs } especially for intermediate risk group

- Stage 1 } localized tumour + **complete excision** + ipsilateral LNs –ve
 → LNs attached to & removed with primary can be positive
- Stage 2A } localized tumour + **incomplete excision** + ipsilateral LNs –ve
- Stage 2B } localized tumour +/- complete excision + **ipsilateral LNs +ve**
- Stage 3 } unresectable tumour crossing midline +/- regional LN involvement
 OR localized unilateral tumour + contralateral regional LNs +ve
 OR midline tumour + bilateral extension
- Stage 4 } any tumour + **distant mets** (LNs, bone, BM, liver, skin, etc)
- Stage 4S } localized primary + **distant mets only in skin, liver, and/or BM (<10%)**
 in infants <1yr of age (NO BONE METS)
 → many of these tumours undergo spontaneous regression

What are the prognostic factors associated with neuroblastoma?

→ “SANDS } stage, age, N-myc, DNA index, shimada stroma-poor

	FAVORABLE	UNFAVORABLE
CLINICAL		
Age	- <1yr of age at Dx	
Site	- non-adrenal primary (thoracic is good)	- adrenal primary
Stage	- stage 1-2 at Dx (75-90% overall survival) - stage 4S at Dx (80-90% overall survival)	- stage 3-4
BIOLOGIC		
N-myc		- presence of N-myc amplification (independent of age, stage)
DNA ploidy	- aneuploidy	- diploid/tetraploid
DNA index	- index >1.0	
Chromosome 1p		- deletion of chromosome 1p
Shimada histology		- stroma-poor tumours

Which 4-S neuroblastoma patients have very poor outcomes?

→ **most do well (80-90% overall survival) BUT these poor risk 4S pts have bad survival**

- 1) elevated serum enolase (>100 nmol/mL)
- 2) elevated ferritin (>280 ng/mL)
- 3) elevated urinary dopamine (>2500 nmol/mmol creat)
- 4) N-myc amplification
- 5) chromosome 1p deletion

What are the goals of surgery for neuroblastoma?

- 1) make Dx
 - 2) stage tumour
 - 3) excise tumour if localized
 - 4) provide tissue for biologic studies
- \ / neo-adjuvant CHEMO prior to resection allows
preservation of vital structures

What is the recommended treatment of neuroblastoma?

→ **based on risk group } determined based on age, stage, N-myc status, grade, DNA ploidy**

- 1) Low-risk disease (stages 1, 2, and 4S)
 - **observation alone** } for some stage 1 and some 4S pts w/ favorable biomarkers
→ N-myc most important
 - **surgical excision** } **>90% disease-free survival with surgery alone**
} may be adequate for stage 4S (favorable biomarkers in most)
 - CHEMO } ONLY if recurrence or unfavorable biomarkers
→ N-myc amplification, unfavorable histology, etc
} neoadjuvant in attempt to preserve vital organs (eg kidney)
} cisplatin + doxorubicin + etoposide + cyclophosphamide (PDEC)
 - minimal role for RADs } only if failed primary or secondary chemo
- 2) Intermediate & High-risk disease (stages 3 and 4)
 - high risk group gets more intensive therapeutic regimes
 - **CHEMO** } **should always be given before surgery**
→ Sx delayed 13-18wks after initiation of chemo
→ tumours are smaller & firmer (less risk of rupture/hemorrhage)
} cyclophosphamide + doxorubicin + cisplatin + etoposide
} ↑s survival and ↓s recurrence
} ↑s likelihood of complete resection and ↓s adjacent organ injury/removal
} for high-risk may need to use BM-ablative CHEMO + autologous BMTx
 - surgical resection } controversy regarding extent of resection required
} may be some benefit to radical resection even in stage 4
→ debulking prior to initiation of systemic Rx
→ especially if considering chemo + autologous BMTx
} watch for diarrhea after resection of extensive tumour around celiac axis
→ due to resection of autonomic nerves
 - RADs (15-30 Gy) } for local control of unresectable or partially resected tumours
} may have role in tumour debulking prior to chemo + BMTx

What are the management options for SC compression from neuroblastoma?

- 1) **CHEMO** } **1st line**
- 2) decompressive laminectomy } reserved for progressive neuro deterioration despite chemo
- 3) RADs } generally avoided due to adverse effects on growth of spine
→ similar outcomes for all modalities } most patients with severe motor deficits recover little function

What are some innovative biologic therapies for neuroblastoma?

- 13-cis-retinoic acid } biological modifier (chemo-sensitizer)
- vaccine and Ab therapy } against Go2 cell surface marker
- anti-angiogenic therapy
- use of radioactive ¹³¹I-MIBG

What are the 3 main histologic subtypes of RMS?

- 1) embryonal } **most common subtype** → **accounts for most of GU RMS tumours**
 - } loss of heterozygosity on chromosome 11p15 (IGF-2 gene)
 - } **spindle cell variant** (leiomyomatous variant) often seen in paratesticular region
 - associated with excellent survival
 - } **botryoid variant often seen in bladder or vagina (hollow organs)**
 - associated with excellent survival
 - } DOES NOT stain for myogenin
- 2) alveolar } **uncommon in GU system** (more common in trunk and extremities)
 - } **associated with worse prognosis**
 - higher rate of local recurrence and spread to LNs, BM, and distant mets
 - } translocation b/w chromosome 1 (PAX7) or 2 (PAX3) and chromosome 13 (FKHR)
 - PAX3-FKHR has bad prognosis; PAX7-FKHR has good prognosis
 - } over-expression of MYCN transcription factor associated with adverse outcome
 - } different than other subtypes in that it **STAINS for myogenin**
- 3) undifferentiated } poor prognosis

*** **“pleomorphic RMS” is anaplastic variant of embryonal or alveolar, not own subtype** ***

What are the differences based on primary site of RMS

- bladder } usually are botryoid variant of embryonal subtype \ **80% of bladder**
 - } grow intraluminally & are usually at or near trigone \ **& prostate RMS**
- prostate } tends to occur as a solid mass / **are stage 3 at Dx**
 - } can cause significant bladder distortion /
- paratesticular } >90% are embryonal subtype with good prognosis (spindle cell variant)
 - even alveolar subtypes do well
 - } **60-80% are stage 1 at Dx (compared to 13% of RMS overall)**
 - } usually arises in **distal portion of spermatic cord** & may invade testis
 - } retroperitoneal LNs +ve in up to 20%
- vaginal & vulvar } usually from anterior vaginal wall
 - } vaginal RMS usually embryonal subtype (botryoid variant)
 - excellent prognosis
 - } vulvar RMS may be alveolar
 - still good prognosis though because most are localized
- uterine } >90% are embryonal subtype
 - } originates from cervix or from uterine body

What is the IRSG TGNM staging system used for RMS (CHART)?

→ **based on clinical, radiographic, laboratory & histologic evaluation**

→ **old system included surgical resection details (like neuroblastoma)**

- Stage 1 } **favorable site** (paratesticular, vagina) + no mets
- Stage 2 } **unfavorable site** (prostate, bladder) + small (<5cm) + -ve LNs + no mets
- Stage 3 } **unfavorable site** (prostate, bladder) + **big (>5cm) OR +ve LNs** + no mets
- Stage 4 } any site + **evidence of mets**
- T stage
 - T1 } confined to site of origin
 - T2 } fixation to surrounding tissues
 - <5cm
 - >5cm
- G stage
 - G1 } favorable histology (embryonal, botryoid variant, spindle cell variant)
 - G2 } unfavorable histology (alveolar, undifferentiated, pleiomorphic)
- N stage
 - No } no regional LN disease
 - N1 } regional LNs +ve clinically
- M stage
 - Mo } no distant mets
 - M1 } +ve mets

What is the pre-op evaluation for GU rhabdomyosarcoma?

- work-up of primary } U/S, CT, or MRI
- metastatic work-up } LFTs, CXR + chest CT, BM Bx, bone scan
- cysto + Bx for bladder & prostate
- vaginosiscopy + Bx for vaginal
- D&C for uterine

What are the general principles of management of pediatric RMS?

- **stage 1 & 2 } neoadjuvant CHEMO +/- RADs + surgical resection**
- **stage 3 & 4 } high-risk neoadjuvant CHEMO + wide-field RADs or surgical resection**
- pre-op chemo allows preservation of functional lower GU tract while maintaining high survival rates
- RADs decreases local recurrence rates but can cause result in bladder dysfunction

What are the management options for pediatric RMS?

→ CHEMO IS MAINSTAY OF TREATMENT

1) Bladder & Prostate RMS

- **focus is on bladder preservation**
- **neoadjuvant CHEMORADs + surgical resection**
 - vincristine + actinomycin D + cyclophosphamide (VAC)
 - may avoid anterior pelvic exenteration with neoadjuvant Rx
 - partial cystectomy may be possible in select cases
 - after neoadjuvant Rx or in rare cases that present near dome
 - issue is local recurrence } majority of those that relapse, die
 - attempts made to limit RADs
 - radiated bladders are functionally very poor
 - try to reserve for those getting cystectomy, w/ poor response to CHEMO, or w/ relapse
- bladder augment may be required in patients with contracted bladders post-RADs
- urinary diversion with non-refluxing colon conduit + later continent reconstruction
 - vs continent reconstruction at time of extirpative surgery
 - early reconstruction has risks } unreliable frozen sections in excluding residual disease
 - } Rx of future local recurrence can affect reservoir function

2) Paratesticular RMS

- **radical inguinal orchiectomy + CEMO**
 - vincristine + actinomycin D
 - if violation of scrotum there is a high risk of recurrence & non-regional LN spread
 - needs inguinal exploration + removal of remaining spermatic cord + partial hemiscrotectomy (including scrotal incision)
- **routine RPLND is controversial } NOT RECOMMENDED if good imaging**
 - high complication rate
 - any microscopic mets can be treated with chemo
- **if >10yrs of age, higher risk of retroperitoneal relapse**
 - perform ipsilateral RPLND for staging prior to chemo
 - if +ve nodes, then high-dose CEMO + RADs
 - if nodes -ve, just CEMO
- if +ve retroperitoneal LNs, RPLND + as above
 - if huge burden of disease, consider neoadjuvant CEMO to preserve organs

3) Vaginal & Vulvar RMS

- **focus is on vaginal preservation**
- **CHEMO +/- RADs +/- surgical resection**
 - if residual disease on Bx post-chemo, they get RADs or Sx
 - partial vaginectomy or vaginectomy + hysterectomy

4) Uterine RMS

- **CHEMO +/- RADs +/- surgical resection**
 - if residual disease on Bx post-chemo, they get RADs or Sx
 - chemo alone may spare the patient local therapy

What are the prognostic factors for GU RMS?

- 1) site } paratesticular & vagina better than prostate & bladder
- 2) size of tumour } <5cm better
- 3) **stage (most predictive of outcome)** } **presence of mets, regional LN status**
- 4) histology } alveolar, undifferentiated, pleiomorphic subtypes are associated with poor outcomes
- 5) age at Dx } survival worse if <1yr old or >10 yrs old
 - high risk of retroperitoneal relapse if >10yrs of age
 - **should have staging RPLND before chemo if >10yrs old**

How successful is treatment of RMS?

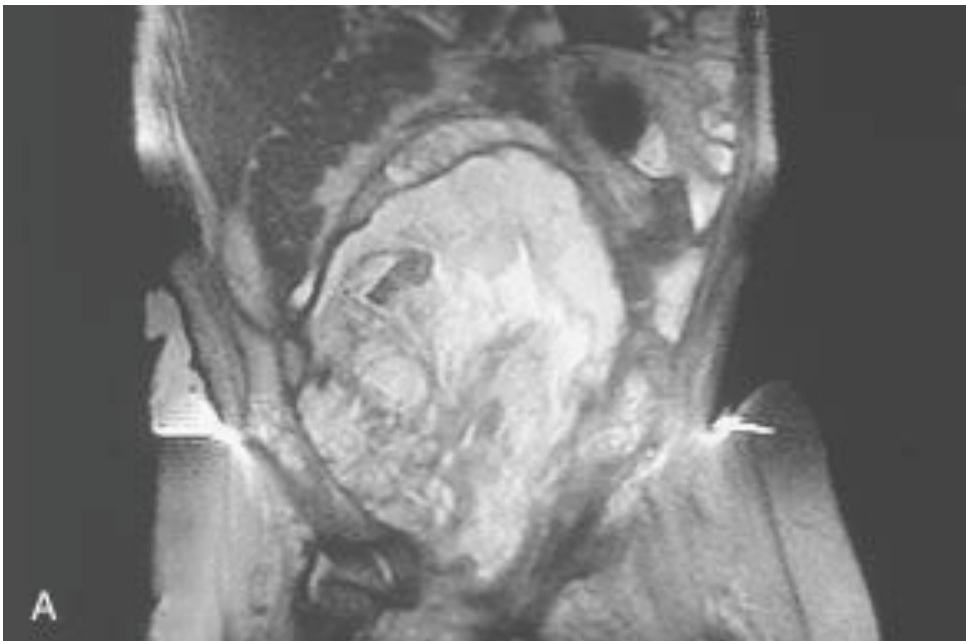
- bladder } >85% 5-yr survival in low risk (response to chemo), low stage disease
 - } worse survival if no RADs given
 - } better survival if botryoid variant (>90% 10-yr survival)
- prostate } worse prognosis
- paratesticular } 90% survival for chemo + orchiectomy
 - } recurrence more common in adolescents

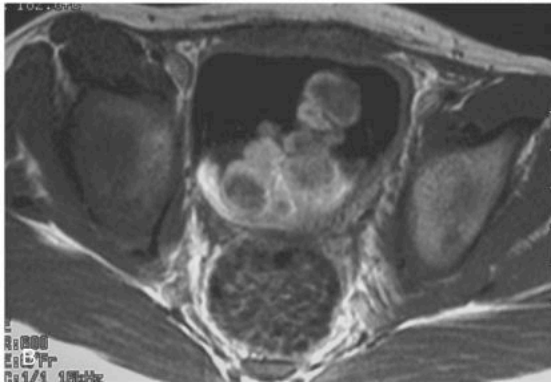
What is the significance of mature RHABDOMYOBLASTS on post-treatment Bx?

- **can safely observe these patients**
- very low risk of recurrence

What other bladder tumours are seen in kids?

- TCC } rare in kids
 - } most are low grade & low stage
 - } likely related to hx of cyclophosphamide or in patients with bladder augments
- nephrogenic adenoma } due to metaplastic response to chronic inflammation
 - } uncommon to recur
- benign fibroepithelial polyp of prostatic urethra } most common benign lesion of prostate
 - } can present w/ obstruction & hematuria

[illegible]



Pathology

**Kid + bladder → think bladder RMS
+ve for desmin stain**

→ IVP & MRI OF BLADDER RHABDOMYOSARCOMA (BOTRYOID) } poor prognostic site
} 80% present w/ stage 3



→ VAGINAL RHABDOMYOSARCOMA (BOTRYOID) } good prognostic site

WILMS' TUMOUR

What is a Wilms' tumour?

- aka nephroblastoma
- **most common primary malignant renal tumour in kids**
 - congenital mesoblastic nephroma (CMN) is most common renal tumour of infants
- **develops from remnant of immature kidney**
- >90% are from somatic mutations restricted to tumour tissue
 - not Knudson's 2-hit genetic mutation
 - **only ~10% are genetic**
- can rarely have extra-renal Wilms' tumours
 - from displaced metanephric elements or mesonephric remnants

What is the epidemiology of a Wilms' tumour?

- accounts for 6-7% of all childhood cancers
- usually affects young kids } **>80% present before 5yrs of age**
- **only 5-7% have bilateral tumours** } usually present earlier than unilateral, unicentric cases
- no sex predilection } slightly more common in F in N. America
- tends to present slightly earlier in M
- **highest incidence among blacks & lowest among asians**
- 1-2% have a family hx } earlier age of onset, increased likelihood of bilateral tumours

What chromosome abnormalities are associated with Wilms' tumour?

- **WT1** gene on chromosome **11p13** } WAGR and DDS
- **WT2** gene on chromosome **11p15** } BWS
- FWT1 gene on chromosome 17q12 \ familial cases
- FWT2 gene on chromosome 19q13 / of Wilms'
- **mutation of tumour suppressor gene p53 (chromosome 17)** \
- **loss of chromosome 16q** } **found in ~20% of Wilms'** } poor prognosis
- **loss of chromosome 1p** } **found in ~10% of Wilms'** /

What anomalies are associated with Wilms' tumour?

- 1) GU anomalies
- 2) syndromes } non-overgrowth (DDS & WAGR)
 - } overgrowth (BWS, hemihypertrophy, Perlman, Soto, Simpson-Golabi-Behmel, etc)

What GU anomalies are associated with Wilms' tumour (CHART)?

- 4.5% have GU anomalies
- **UDT - most common anomaly associated with Wilms (40%)**
- hypospadias (13%)
- renal fusion anomalies (eg horseshoe kidney)
- anomalies of Mullerian duct structures (eg duplication of cervix or bicornuate uterus)

Which syndromes are associated with an increased incidence of Wilms' tumour?

→ NON-OVERGROWTH SYNDROMES

- 1) Denys-Drash syndrome
 - **Wilms' + male pseudohermaphroditism (MGD) + renal mesangial sclerosis (CRF)**
 - develop ESRD (nephrotic type – congenital nephrosis)
 - associated with mutation in chromosome 11p13 (loss of one copy of WT1 gene)
 - mainly in XY individuals
- 2) WAGR syndrome
 - **Wilms' + Aniridia + GU anomalies + Retardation**
 - associated with deletion in chromosome 11p13 (abN PAX6 gene near WT1 gene)
 - more likely to have bilateral tumours & presents at an earlier age
 - more prone to develop ESRD

➔ OVERGROWTH SYNDROMES

- 3) Beckwith-Wiedemann syndrome
 - **macroglossia + hemihypertrophy + organomegaly (kidney, liver) + omphalocele + adrenal Ca + medullary renal cysts + hypoglycemia (from pancreatic β cell hyperplasia)**
 - most cases are sporadic (loss of heterozygosity of WT2 gene) } 15% genetic (AD)
 - more likely to have bilateral tumours
 - excellent prognosis
- 4) Hemihypertrophy w/o BWS
 - **hemihypertrophy is 2nd most common anomaly associated with Wilms**
- 5) Perlman syndrome
 - nephromegaly + renal dysplasia + macrosomia + UDT + facial deformities
- 6) Soto syndrome
 - cerebral gigantism + retardation + hypertelorism
- 7) Simpson-Golabi-Behmel syndrome (“bulldog syndrome”)
 - stocky appearance + bulldog facies

*** screening U/S's recommended for kids with aniridia, hemihypertrophy, & BWS q3-4 mos ***

What are the histologic features of Wilms' tumour?

- characterized by **tremendous histologic diversity**
- gross } rim/pseudocapsule of compressed atrophic renal parenchyma
 - } soft and friable tumour with frequent necrotic or hemorrhagic areas
 - } **most are unicentric but ~10% are multicentric**
- microscopic
 - 1) **“Classic” Wilms’ } composed of blastemal cells, epithelial cells, & stromal cells**
 - most are “triphasic” but some are biphasic, etc
 - mostly epithelial = less aggressive tumours
 - BUT may not respond well to chemo
 - mostly blastemal = highly aggressive tumours
 - BUT responds to chemo
 - **presence of nephrogenic rests (NRs) assoc’d w/ bilateral Wilms’**
 - nuclear atypia associated with poor outcomes
 - 2) **Anaplastic Wilms’ } characterized by 3 histologic abN’ties (see below)**
 - **presence of diffuse anaplasia assoc’d w/ resistance to chemo** (focal better)
 - **poor outcomes } rarely seen if <2yrs of age but found in 15% of kids >5yrs**
 - **WORST PROGNOSTIC FACTOR**

What are the 3 histologic abnormalities that characterize anaplastic Wilms' tumour?

- 1) nuclear enlargement (3-4x adjacent cells)
- 2) hyperchromasia of enlarged nuclei
- 3) abN mitotic figures

What is the significance of Nephrogenic Rests in Wilms' tumour (includes CHART)?

- precursor lesion } **associated with bilateral Wilms' tumours**
- 2 different types
 - Intralobar (ILNRs) } associated with WAGR and DDS
 - found in >85% with aniridia
 - } associated with younger age at presentation
 - Perilobar (PLNRs) } associated with BWS
 - found in ~80% w/ BWS and bilateral Wilms' tumour
- kids <1yr of age diagnosed with Wilms' tumour that also have NRs (**especially PLNRs**)
are **associated with increased risk of developing contralateral disease**
- **presence of multiple NRs is called "nephroblastomatosis"**

What is the work-up for a Wilms' tumour?

1) history & P/E

→ **MOST KIDS SEEM WELL (unlike neuroblastoma, where they are sick)**

- abdominal mass (>90%) or abdo pain
- gross hematuria
- fever
- HTN (25%) } from increased renin
- acute abdomen } rupture of tumour with hemorrhage into peritoneum
- atypical presentation from extension/compression of IVC } varicocele, hepatomegaly, ascites, CHF
- may have associated findings } eg UDT, hemihypertrophy, aniridia, GU anomalies

2) Lab tests

- CBC, lytes, creatinine, LFTs, Ca profile, urinalysis } **acquired vWD found in 8%**
} ↑'d calcium in CMN & RTK

3) imaging

→ **precise Dx cannot be made on pre-op imaging alone**

→ all solid renal tumours in kids have some common radiologic features

→ wrong Dx (not Wilms') in 5-10%

- U/S } determines solid vs cystic renal mass
} can often identify caval thrombus if present
- chest + abdo/pelvis CT scan } staging
} presence of N contralateral kidney prior to Nx
- MRI } can identify caval thrombus if U/S is equivocal
- bone scan +/- skeletal survey } to r/o bone mets



→ CT SCAN OF LEFT SIDED WILMS' TUMOUR

What is the DDx of a Wilms' tumour?

- congenital mesonephric nephroma (CMN) } most common renal tumour in young kids (overall)
- rhabdoid tumour of the kidney (RTK)
- clear cell sarcoma of the kidney (CCSK)
- renal lymphoma (can be bilateral)
- RCC
- neuroblastoma

What are the common sites of distant mets in kids with Wilms' tumour?

- **lung (most common)**
- bone
- liver
- brain

What is the COG Staging system used for Wilms' tumour (CHART)?

→ **Children's Oncology Group (N. American approach to Wilms' tumours)**

→ **based on surgical & histopathologic findings**

→ presence of nephrogenic rests no included in staging

- Stage 1 } limited to kidney + completely excised + intact renal capsule + no rupture
- Stage 2 } tumour beyond kidney + completely excised +/- extrarenal vessel thrombus
- Stage 3 } residual tumour confined to abdomen
 - incomplete excision OR +ve LNs OR tumour spillage/rupture OR peritoneal implant
 - Biopsy makes automatically stage 3
- Stage 4 } hematogenous mets to lung, liver, bone, brain, etc
- Stage 5 } bilateral renal involvement

List some new prognostic factors in Wilms' tumour?

→ with more effective Rx, traditional factors less able to predict risk of progression or relapse

- less able to stratify FH patients for Rx

→ **classic prognostic factors } histology (anaplastic, mostly blastemal, clear cell sarcoma of kidney, rhaboid tumour of kidney are BAD)**

→ **most important factor**

} stage (lower better)

- 1) chromosomal abnormalities (loss of chromosome 1p, 16q, p53)
- 2) high telomerase activity
- 3) DNA content
- 4) cytokines (lung mets more common in VEGF +ve tumours)
- 5) tumour markers (HA, FGF, plasma renin)

What are the principles of surgical management for Wilms' tumour?

→ Radical Nx

- assess entire abdomen for evidence of mets } transperitoneal approach
- **sampling of suspicious LNs essential**
- **no role for exploration of contralateral kidney if good pre-op CT/MRI**
- complete excision w/o contamination is essential } **6-fold higher relapse rate with tumour spillage**
- lower complication rate if Nx done after neoadjuvant CHEMO

What are the principles of CHEMO for Wilms' tumour?

→ **everyone should get CHEMO } NWTSG-5**

} differing schools re: neoadjuvant VS adjuvant

→ vincristine + actinomycin D

→ add doxorubicin if ≥stage 3

→ add cyclophosphamide if diffuse anaplasia in ≥stage 2-4

- COG/N. America } adjuvant in most & neoadjuvantly for certain cases (eg Stage 5)
- SIOP/Europe } neoadjuvant chemo given to all, followed by surgery
- pulse-intensive CHEMO shown to be equivalent while decreasing cost of Rx
- differentiation of tumour occurs after chemo } stromal & epithelial dominant tumours seen more commonly after CHEMO

What are the principles of RADs for Wilms' tumour?

→ NO radiation if Stage 1 Wilms' (FH and anaplasia)

→ given if high-risk of relapse } high stage (3-4) or presence of anaplasia in stage 2-4

→ also option for local recurrence if PNx done

- **avoid unnecessary RADs**

What are the indications for NEOADJUVANT CHEMO for Wilms' tumour (as per COG)?

- neoadjuvant chemo is standard in Europe (SIOP) } only for these indications as per NWTSG
- **majority of shrinkage occurs in first 4 weeks**
- **biopsy performed before initiation of chemo**
- 1) stage 5 (bilateral tumours ... including NRs) \ to decrease risk of
- 2) solitary kidney / renal failure
- 3) inoperable tumour at time of Sx } should not be based on pre-op imaging
→ local tumour extension can be overestimated
- 4) tumour extension into IVC above hepatic veins

What are the recommendations for the management of Wilms' tumours as per NWTSG-5?

- goal is to reduce morbidity of Rx in low-risk patients while reserving more intensive Rx for high-risk patients with poor survival rates
- presence of favorable histology (FH) dictates treatment to a significant degree
- **Stage 1 (all) and Stage 2 (FH)**
 - a) RADICAL Nx + sampling of suspicious LNs
 - b) pulse-intensive CHEMO } vincristine + actinomycin-D (VA x 18wks)
 - c) No RADs
- **Stage 2-4 (focal anaplasia) and Stage 3-4 (FH)**
 - a) RADICAL Nx + sampling of suspicious LNs
 - b) pulse-intensive CHEMO } vincristine, actinomycin-D, doxorubicin (VAD x 24wks)
 - c) 10.8 Gy of RADs to abdomen } add 12Gy to both lungs if stage 4 (FH)
- **Stage 2-4 (diffuse anaplasia) and Stage 1-4 (clear cell sarcoma of kidney)**
 - a) RADICAL Nx + sampling of suspicious LNs
 - b) pulse-intensive CHEMO } vincristine, actinomycin-D, doxorubicin (VADEC x 24wks)
} add cyclophosphamide, etoposide
 - c) 10.8 Gy of RADs to abdomen + 12 Gy to both lungs
- **Stage 1-4 (rhabdoid tumour of kidney)**
 - a) RADICAL Nx + sampling of suspicious LNs
 - b) pulse-intensive CHEMO } carboplatin, etoposide, cyclophosphamide (CEC)
 - c) RADs given to all

What are the RFs for local recurrence of Wilms' tumour?

- tumour spillage \
- unfavorable histology \ 43% survival at 2yrs after
- incomplete resection / local recurrence in abdomen
- no LN sampling /
- +ve LNs /

What is the management of bilateral Wilms' tumour (Stage 5)?

- 1) initial Bx before pre-op CHEMO } moving towards NOT doing pre-op Bx now
 - VADEC
 - confirm Wilms' & define histology
 - Nx can be avoided in ~50% of patients that undergo this strategy
- 2) repeat imaging after 6weeks of chemo
 - assess feasibility of partial Nx
 - if no response, perform or repeat an open Bx
 - if blastemal-predominant or anaplastic Wilms' on repeat Bx, need to Δ chemo
 - 12 more weeks of different chemo regime
- 3) reassess to see if partial Nx possible on either or both kidneys
 - bilateral Radical Nx if tumours fail to respond to chemo & rads
 - if ESRD develops despite partial Nx, must remove remaining renal mass before Tx
- 4) long-term close f/u essential } late relapses can occur (>4yrs later)

What is the role of Partial Nx for unilateral Wilms' tumours?

→ CONTROVERSIAL

- most tumours are too large for Partial Nx at diagnosis
- after pre-op CHEMO, partial Nx possible in 10-15%
- **should be reserved for select cases**
 - 1) **bilateral tumours (stage 5)**
 - 2) **tumours in solitary kidney**
 - 3) **tumours in kids with renal insufficiency**
 - 4) **kids with syndromes associated with renal failure (Denys-Drash, WAGR)**

What are the arguments AGAINST partial nephrectomy?

- 1) low rate of future renal failure } mainly occurs in those with syndromes that predispose them to renal failure anyways (eg DDS, WAGR)
- 2) local recurrence rate is 8%
- 3) intra-abdominal relapse associated with markedly decreased survival (40%)
- 4) many tumours are too large for partial Nx

How common is renal failure with Wilms' tumours?

- unilateral without GU anomalies } 1%
- bilateral Wilms' } 10-12%
- Denys-Drash or WAGR } >50%
 - can consent for upfront nephrectomy as most will develop ESRD

What are some of the late complications associated with the treatment of Wilms' tumour?

→ RADs

- decreased stature
- scoliosis
- hypogonadism +/- delayed sexual maturation
- temporary azoospermia
- ovarian failure
- future risk of low birth wt, prematurity, & congenital malformations in offspring
- 2nd malignancies (liver Ca, AML)

→ CHEMO

- hypogonadism
- azoospermia
- CHF (from doxorubicin)

What are the features that differentiate Wilms' tumour from Neuroblastoma?

	WILMS'	NEUROBLASTOMA
general appearance	Looks WELL	looks SICK
Age	Older (3-4yrs)	younger (1-2yrs)
associated syndromes/GU anomalies	Yes	No
Relation to vessels	can invade	encases
metastases	uncommon (5%)	common (>50%)
spontaneous regression	No	Yes (stage 4S)
abdominal mass	DOES NOT cross midline	CROSSES midline
calcifications on imaging	rare (5% - eggshell)	common (50% - stippled)
MIBG scan	-ve	+ve
MRI (T2)	dark	bright

What are the recommended f/u imaging studies for kids with renal tumours?

Tumor Type		Study	Schedule after Therapy
Favorable-histology Wilms' tumor			
	Stage I anaplastic Wilms' tumor	Chest films	6 wk and 3 mo postop, then q3 mo × 5, q6 mo × 3, yearly × 2
	Irradiated patients only	Irradiated bony structures[*]	Yearly to full growth, then q5yr indefinitely[†]
	Without NRs, stages I and II	Abdominal ultrasound	Yearly × 3
	Without NRs, stage III	Abdominal ultrasound	As for chest films
	With NRs, any stage[‡]	Abdominal ultrasound	q3 mo × 10, q6 mo × 5, yearly × 5
	Stage II and III anaplastic	Chest films	As for favorable histology
		Abdominal ultrasound	q3 mo × 4, q6 mo × 4
Renal cell carcinoma		Chest films	Like favorable histology
		Skeletal survey and bone scan	Like CCSK
CCSK		Brain MRI and/or opacified CT	When CCSK is established, then q6 mo × 10
		Skeletal survey and bone scan	As for favorable histology
		Chest films	
Rhabdoid tumor		Brain MRI and/or opacified CT	As for CCSK
		Chest films	As for favorable histology
Mesoblastic nephroma[§]		Abdominal ultrasound	q3 mo × 6

Modified from D'Angio GJ, Rosenberg H, Sharples K, et al: Position paper: Imaging methods for primary renal tumors of childhood: Cost versus benefits. Med Pediatr Oncol 1993;21:205-212.

List chemotherapeutic agents used for pediatric malignancies.

- 1) Neuroblastoma
 - PDEC
 - cisplatin
 - doxorubicin
 - etoposide
 - cyclophosphamide
- 2) RMS
 - VAC
 - vincristine
 - actinomycin D
 - cyclophosphamide
- 3) Wilms'
 - VADEC
 - vincristine
 - actinomycin D
 - doxorubicin
 - etoposide
 - cyclophosphamide
 - CEC for RTK
 - carboplatin
 - etoposide
 - cyclophosphamide

ALKYLATING AGENTS

Eg cisplatin, carboplatin, cyclophosphamide, ifosfamide, thiotepa, estramustine, nitrogen mustard

Mode of action: directly damages DNA

Toxicities:

Cisplatin → nephrotoxicity, ototoxicity, **peripheral neuropathy**, mild cytopenia, N/V, Raynaud's, gonadal dysfxn

Carboplatin → ototoxicity, nephrotoxicity, hepatitis, hypoMg, hypoK, peripheral neuropathy, **myelosuppression** (worse than cisplatin)

Cyclophosphamide → cytopenia, **hemorrhagic cystitis**, cardiomyopathy, spermatogenic arrest, SIADH

ANTIMETABOLITES }}} “GM-5”

Eg MTX, gemcitabine, 5-FU

Mode of action: interfere with DNA and RNA division

Toxicities:

MTX → myelosuppression, nephrotoxicity, pulmonary fibrosis (minimized by leukovorin), stomatitis

Gemcitabine → nephrotoxic, hepatotoxic, cytopenia, alopecia

ANTI-TUMOUR ANTIBIOTICS }}} “-mycin's”

Eg bleomycin, doxorubicin/adriamycin, mitoxantrone, mitomycin C, actinomycin-D

Source: from byproducts of fungus Streptomyces

Mode of action: interfere with enzymes involved in DNA replication, preventing RNA synthesis

Toxicities:

Bleomycin → **pulmonary fibrosis**, pneumonitis fevers and chills (**NO MYELOSUPPRESSION**)

Doxorubicin/adriamycin → cytopenia, **cardiotoxicity**

Mitoxantrone → **cardiotoxicity**, cytopenia, mucositis

MITOTIC INHIBITORS/PLANT ALKALOIDS }}} “VET”

Eg vinca alkaloids (vinblastine, vincristine), taxanes (docetaxel), etoposide

Source: plant derivatives

Mode of action: antimicrotubule agents

Toxicities:

Docetaxel → cytopenia, redness/soreness of **palms and soles**, peripheral neuropathy, fluid retention

Vinblastine → neurotoxicity, BM suppression, glossitis

Vincristine → neurotoxicity, alopecia (**NO MYELOSUPPRESSION**)

Etoposide → mucositis, hepatitis, pneumonia, BM suppression, **secondary malignancies**

OTHER RENAL TUMOURS

What is the DDx of renal tumours in kids?

→ BENIGN

- congenital mesoblastic nephroma (most common renal tumour in young infants)
- AML
- fibroepithelial polyp
- oncocytoma
- solitary multilocular cyst
- cyst, hemorrhage, etc

→ MALIGNANT

- Wilms' tumour (most common malignant renal tumour in kids)
- clear cell sarcoma of kidney (CCSK)
- rhabdoid tumour of kidney (RTK)
- cystic partially differentiated nephroblastoma
- metanephric adenofibroma
- RCC
- TCC

What is clear cell sarcoma of the kidney (CCSK)?

- accounts for 3% of renal tumours in kids } 1-3 yrs of age
- classic pattern consists of cellular lesion of polygonal cells w/ round oval nuclei having a delicate chromatin pattern and indistinct nucleoli
→ can mimic Wilms' tumour, RTK, and CMN
- **can occur in extra-renal locations**
- **tends to metastasize to bone** } **kid with abdo mass + limp**
- **almost never bilateral**
- even stage 1 CCSK is associated with increased rates of relapse
→ **post-op RADs given even to all Stage 1 lesions**
- different chemo regime for CCSK
→ vincristine, doxorubicin, cyclophosphamide, and etoposide
- **long-term f/u needed**
→ 30% of relapses occur >3yrs after Dx

How does CCSK differ from Wilms' tumour?

CCSK	Wilms'
- mostly bone & brain mets	- mostly lung & liver mets
- unilateral only	- can be bilateral
- not associated w/ congenital anomalies	- associated congenital anomalies (aniridia, hemihypertrophy, etc)
- RADs for all stages	- no RADs for stage 1 disease

What features of CCSK give a favorable prognosis?

- lower stage
- younger age at Dx
- treatment with doxorubicin
- absence of tumour necrosis

What is rhabdoid tumour of the kidney (RTK)?

- **most aggressive & lethal renal tumour in kids**
 - early age at Dx (median <16 months)
 - advanced stage
 - resistant to chemo
 - **high mortality rate (80%)**
- accounts for 2% of renal tumours in kids
- **considered a sarcoma of the kidney but the cell type of origin is unknown**
- characterized by large, uniform cells w/ abundant acidophilic cytoplasm, often containing a discrete zone of pale eosinophilia, made of fibrillary inclusion bodies & large nuclei w/ prominent nucleoli
- **can occur in extra-renal locations**
- associated with deletions & somatic mutations in the INI1 gene on chromosome 22
 - does not stain for products of INI1 gene
- **tends to mets to brain** but also can develop 2nd primary tumours in the brain
 - cerebellar medulloblastomas, pineoblastomas, neuroblastomas, & subependymal astrocytomas

What is Congenital Mesoblastic Nephroma (CMN)?

- **the most common renal tumour in kids <3mos**
 - **mean age at Dx is only 3.5 months**
 - **benign vs malignant variant**
- very firm on gross examination & resembles leiomyoma on gross
- 3 different subtypes } classic, cellular, mixed
 - **“cellular variant” has higher rate of recurrence & mets**
- involves translocation of ETV6 gene (chromosome 12) with NTRK3 gene (chromosome 15)
- Rx → **usually excellent outcome w/ radical surgery only } Partial Nx not recommended**
 - CHEMO & RADs only used for adjuvant Rx of incompletely resected cellular variants

What is the DDX of a solid “renal mass” seen on FETAL U/S?

- renal masses are unusual in fetal GU tract
- 1) **congenital mesoblastic nephroma (most common)**
 - benign tumour that usually replaces entire kidney with homogeneous round mass
 - may be associated with **polyhydramnios**
 - can't r/o malignancy so early post-natal removal is recommended
- 2) neuroblastoma
 - may appear as renal mass or cystic suprarenal masses } prenatal MRI can help with Dx
 - need to r/o metastatic neuroblastoma } total body examination needed
- 3) Wilms' tumour
 - rarely described prenatally

What is a solitary multilocular cyst?

- aka “multilocular cystic nephroma”
- **uncommon, BENIGN, renal tumour**
- bimodal distribution } 50% found in young boys
 - } also found in young adult women
- usually unilateral
- well-encapsulated multilocular tumour w/ various-sized cysts compressing surrounding renal tissue
 - only mature cell types found within septa of cyst wall
- Rx → Nephrectomy } cure
 - Partial Nx } must do frozen section to r/o cystic Wilms'

What is a cystic, partially differentiated nephroblastoma (Wilms')?

- usually occurs in first 2 yrs of life } very similar to solitary multilocular cyst
- Rx → Nephrectomy } almost 100% survival
 - partial nephrectomy
 - CHEMO for stage 2 disease

What is a metanephric adenofibroma?

- tumour with prominent stromal features } can resemble CMN
 - can contain areas of Wilms' tumour and papillary RCC
 - thought to be derived from ILNRs
- Rx → Nx + Wilms' tumour CHEMO (vincristine + dactinomycin +/- doxorubicin)

How common is RCC in kids?

- **most common renal malignancy in 2nd decade of life** } only 5% of all RCCs are in kids
 - usually presents as abdo mass +/- hematuria
 - **can't be distinguished on imaging from Wilms' tumour, etc**
 - **higher incidence of papillary RCC in kids**
 - usually have translocation involving TFE gene on chromosome X
 - **also higher incidence of medullary RCC in some kids**
 - sickle cell kids } highly lethal tumours
 - **overall survival, stage for stage, is better in kids**
- Rx → Radical Nx or Partial NX } complete resection is essential
- younger age at Dx is favorable
 - +ve regional LNs not as bad prognosis as in adults
 - like adults, not chemosensitive & not radiosensitive

How common are AMLs in kids?

- **only rarely seen in kids**
 - clear association with Tuberous Sclerosis complex (TSC) } develops in 80% of TS patients
 - usually B/L in these kids
 - also see simple cysts, PCKD, and RCC
 - risk of bleeding significantly increases in AMLs >4cm
- Rx → nephron-sparing approach for those with TS
- embolization or Partial Nx for growing lesions or lesions >4cm

TESTICULAR TUMOURS

What is the epidemiology of testicular tumours in kids?

- uncommon } only 1-2% of all solid tumours in kids
- **benign lesions represent a greater percentage in kids than in adults } ~75% are benign**
- incidence peaks at 2yrs of age, then tapers after 4yrs of age, then starts to rise again at puberty
- rare in black & asian kids

What is the DDx of pre-pubertal testicular tumours (CHART)?

- 1) Germ cell tumours
 - NSGCTs } yolk sac (most common malignant), **teratoma (most common overall now!!)**, mixed
 - seminoma
- 2) gonadal stromal tumours (**more common in kids than adults**)
 - Leydig cell (don't metastasize in kids)
 - Sertoli cell
 - Juvenile granulosa cell
 - mixed
- 3) gonadoblastoma
- 4) tumours of supporting tissues
 - fibroma
 - leiomyoma
 - hemangioma
- 5) lymphomas and leukemias
- 6) tumour-like lesions
 - **epidermoid cysts**
 - hyperplastic nodule secondary to CAH
- 7) secondary tumours
- 8) tumours of the adnexa

What chromosomal abnormalities have been found in kids with GCTs?

- most frequent chromosomal abN is an isochromosome of 12p
- also see loss of chromosome 11, 13, and 18 and gain of chromosomes 7, 8, and X
- benign teratomas } NO abnormalities
- yolk sac } gains of chromosome 1q and 3

What are the etiologic RFs associated with testicular cancer?

- **intersex disorder** (eg AIS, gonadal dysgenesis with Y chromosome)
 - 10% incidence by 20yrs of age
 - can get both GCTs and gonadoblastoma
 - seminoma rare in kids except with gonadal dysgenesis
 - gonadectomy recommended for gonadal dysgenesis kids with Y chromosome
 - 6% incidence of ITGC neoplasia (CIS) noted in kids with intersex
- UDT
 - link is not as strong in kids
 - mostly in boys with bilateral UDT
 - seminoma is the most common type
- CIS (intratubular germ cell neoplasia)
- Family Hx
- maternal hormonal exposure (DES in utero)
- race
 - more common in whites and Jews

What are the different pathologic types of pediatric testicular cancer?

- totipotent germ cells evolve into seminoma or embryonal carcinoma
- embryonal carcinoma then can differentiate into teratoma, yolk sac, and choriocarcinoma
- Yolk sac tumours
 - most common MALIGNANT testis tumour in kids
 - hemorrhage unusual
 - see epithelial & mesenchymal cells in organoid pattern
 - get **Schiller-Duval bodies & Embryoid bodies**
 - stains for AFP
- teratoma
 - **NOW most common testis tumour in kids OVERALL (new!)**
 - mature, immature, and malignant
 - multiple cysts present
 - cartilage, bone, mucous glands, or muscle may be evident
 - may be associated with epidermoid cysts

What are the 2 main pathologic types of gonadal stromal tumours?

- Leydig cell tumour
 - well encapsulated with compression of adjacent testis tissue
 - steroid production by tumour stains yellow to brown
 - see **Reinke's crystals** in 40% of tumours
 - no increased mitotic figures or other features suggestive of malignancy in kids
- Sertoli cell tumour
 - usually no hemorrhage or necrosis
 - histology doesn't correlate w/ outcomes } often has high mitotic rates, nuclear pleomorphism, & increased cellularity but does well
- granulosa cell

What is the significance of testicular CIS?

- **found in adolescent cases of GCTs but NOT in younger kids with yolk sac tumours**
- **also found in kids with AIS & gonadal dysgenesis**
- NOT associated with cryptorchidism, as is seen in adults
- Rx → repeat Bx after puberty in pre-pubertal kids with CIS

How do testicular tumours present in kids?

- painless mass } most common finding
- acute abdo pain } can be initial symptom of torsion in an abdominal undescended testis w/ a tumour
- **think cancer if very tense hydrocele** } 25% of malignant tumours have reactive hydrocele

What are the U/S findings of a testis tumour?

- cannot reliably distinguish benign from malignant tumours on U/S
- anechoic cystic lesion may suggest benign lesion (eg teratoma, cystic granulosa cell tumour)
- heterogeneous mass w/ concentric rings of alternating hypoechoic & hyperechoic layers ("onion-skin")
may suggest epidermoid cyst

What is the significance of elevated AFP in a kid with a testicular mass?

- **if N, can consider partial orchiectomy**
 - **if elevated, the tumour is considered to contain yolk sac elements**
 - made by fetal yolk sac, liver, and GI tract } half life is ~5days
 - AFP levels may be elevated in infant boys but don't always represent the presence of a malignant tumour or persistent disease after orchiectomy
 - can't apply N adult reference value because AFP synthesis continues after birth
 - N adult levels (<10 mg/mL) are not reached until ~8 months of age
- *** **β-hCG rarely elevated in prepubertal testicular tumours** ***

What is the COG staging system used for testis tumours in kids?

→ **based on pathology and tumour markers**

- Stage 1 } tumour limited to testis + complete resection + no evidence of disease elsewhere
 } -ve markers post-orchietomy
- Stage 2 } microscopic residual disease present in scrotum or high in spermatic cord
 } tumour rupture or scrotal Bx before complete orchiectomy
 } elevated markers post-orchietomy
- Stage 3 } +ve retroperitoneal LNs
 → if >4cm, then considered mets
 → if 2-4cm, then need Bx to document mets
- Stage 4 } distant mets

How is teratoma treated differently in kids compared to adults?

→ teratoma is the most common testis tumour in prepubertal kids (~50%)

→ mature teratoma

- **benign course in kids } adults can have malignant change & mets**

Rx → if mature teratoma suspected, Partial orchiectomy recommended

- presumptive Dx made on U/S
- inguinal approach
- intra-op frozen sections to confirm

→ immature teratoma

- less common } more common in ovary
- **tend to have benign course**
 → considered malignant in adults
 → may occasionally have foci of malignant cells
- immature testicular teratoma has low risk of relapse (unlike other site)
 → high if incomplete resection, elevated AFP, or small foci of yolk sac

**Rx → observation recommended } risk of relapse generally low
 } recurrence salvaged w/ platinum-based chemo**

What are the most common sites of extra-gonadal GCTs?

- 1) **mediastinum (most common)**
- 2) retroperitoneum
- 3) sacrococcygeal region (most benign)
- 4) pineal gland

What is the significance of epidermoid cysts?

- 3% of pediatric testicular tumours
- **BENIGN monodermal teratoma**
- AFP normal and Dx suggested on U/S
 → heterogeneous mass w/ concentric rings of alternating hypoechoic & hyperechoic layers
 ("onion-skin")

Rx → Partial orchiectomy recommended in kids (and adults)

- inguinal approach
- intra-op frozen sections to confirm

What is the epidemiology of yolk sac tumours in kids?

- **2nd most common pre-pubertal testis germ cell tumour in kids**
 → **most common MALIGNANT testis tumour in kids**
- occurs mainly in kids <2yrs of age
- most common site of mets is the lung (20%)
- mets to the retroperitoneum occurs in 4-6% of kids
- **>90% are seen with stage 1 disease**

What is the w/u for pediatric testicular tumours?

- Hx and P/E
- serum markers } AFP & β hCG (very rare to have elevated β HCG)
- scrotal U/S
- avoid CT scan if possible } benign teratoma most common mass
→ RADs for benign disease

What is the management of pediatric yolk sac tumour?

- radical inguinal orchiectomy
→ curative in most kids
- **routine RPLND and/or adjuvant CHEMO is NOT RECOMMENDED**
- Stage 1 } inguinal exploration
 - if markers +ve } radical orchiectomy
 - if markers -ve } partial orchiectomy with frozen
 - if yolk sac, complete radical orchiectomy
 - if teratoma, can leave testis (unless +puberty, then remove)
 - } if scrotal orchiectomy + negative margins, proximal cord structures must be resected to level of internal inguinal ring
→ hemiscrotectomy unnecessary
- Stage 2 } if persistent elevated markers or evidence of retroperitoneal disease then treat as stage 3
} if previous scrotal Bx, completion orchiectomy + removal of all cord structures
- Stage 3 } if +ve retroperitoneal LNs, CHEMO with BEP (bleomycin, etoposide, cisplatin)
- Stage 4 } chemo (BEP)

What is the recommended surveillance after management of pediatric yolk sac tumour?

- CXR, abdo CT/MRI q1month x 3, then q3months x1, then q6months until 3yrs
- tumour markers and P/E more frequently

What is the management of residual post-chemo retroperitoneal masses?

- uncommon
- RPLND at 12 weeks } to establish histologic diagnosis
 - } if viable tumour, switched to different chemo regime
→ RPLND even for post-chemo elevated markers
(NB – different in adults } would get salvage chemo)

What is the management of gonadal stromal tumours in kids?

→ **more common than in adults**

- 1) Leydig cell tumour
 - **most common of the sex cord tumours**
 - **classic triad } precocious puberty + unilateral testis mass + ↑'d 17-ketosteroids**
 - peak incidence is at age 4-5yrs
 - produces testosterone } can lead to precocious puberty
 - can also produce corticosteroids, progesterone, and estrogens
 - **not malignant in kids**
 - Rx → inguinal orchiectomy
- 2) Sertoli cell tumour
 - develop at an earlier age than Leydig cell tumours
 - not as metabolically active as Leydig cell tumours
 - more common with Peutz-Jeghers syndrome and Carney complex
 - Rx → inguinal orchiectomy
 - testis-sparing procedures in kids
 - r/o retroperitoneal spread

What is the DDX of precocious puberty?

- 1) pituitary lesions
→ should have elevated LH/FSH
- 2) Leydig cell hyperplasia
→ normal levels of urinary 17-ketosteroids
- 3) hyperplastic testis nodules that develop in boys with CAH
→ tend to have B/L nodules
→ get ↑'d urinary ketosteroids & serum 17-hydroxyprogesterone w/ 21-hydroxylase deficiency
- 4) large cell Sertoli cell tumours

What is gonadoblastoma?

- **small BENIGN tumours found in kids with gonadal dysgenesis**
- bilateral in 33% of cases
- tumours are composed of large germ cells (similar to seminoma), sex cord derivatives that resemble immature granulosa and Sertoli cells, and occasionally stromal elements
→ regression of nodules usually seen after glucocorticoid replacement
- **most common tumours found in association with intersex disorders**
→ **associated with the presence of a Y chromosome**
→ **phenotypically 80% are F**
→ occurs in gonadal dysgenesis
→ **>25% risk in kids with mixed gonadal dysgenesis (MGD)**
- **germ cell component of gonadoblastoma is prone to malignant degeneration**
→ usually into seminoma

What is the management of gonadoblastoma in kids?

- Rx → all streak gonads should be removed
→ undescended testes in mixed gonadal dysgenesis should also be removed
→ gonadal dysgenesis raised as female should have gonads removed
→ scrotal testes can be preserved (lower risk of Ca)

How common is leukemia or lymphoma of the testis?

- most common malignancy that spreads to the testis in kids
 - 20% of kids with bulky ALL have testicular relapse } much less likely after systemic chemo
 - follicular lymphoma can occur as a primary tumour in the testis
 - 4% of boys with Burkitt's lymphoma
- routine Bx after chemo NOT recommended

What is testicular cystic dysplasia?

- rare BENIGN lesion
- has multiple small irregular cysts localized in the rete testis
- associated with renal agenesis or multicystic renal dysplasia

- Rx → observation + surveillance
→ testis-sparing surgery

What is the significance of testicular microlithiasis?

- found in >5% of healthy adult males } less common in kids
 - reported to be associated with testis tumours
- Rx → surveillance U/S until adult age

Which patients with testicular microlithiasis are at increased risk of cancer?

- infertile men with atrophic testes + microlithiasis
- known testis cancer + microlithiasis in contralateral testis

- [illegible]

PNL

What are the unique features of pediatric PNL?

- access is gained by interventional radiologists more often
- smaller renal access sheaths & nephroscopes (17-24Fr) are available
- percutaneous access in kids is most commonly used for stones
- irrigation solution must be warmed
 - **hypothermia can occur quickly in kids**
- NS is preferred to prevent dilutional hyponatremia
 - **hyponatremia can occur quickly in kids**
- Holmium:YAG is ideal option for kids
 - U/S is good but large size limits use
 - EHL can perforate collecting system a lot easier in kids
 - lithoclast is another good option (suction included)

Why is SWL preferred over PNL in kids?

- SWL is 1st-line option for large renal stones in kids
- ureter is very distensible in kids
 - allows passage of relatively large stone fragments
- no strict upper limit of stone burden as in adults

What are the indications for PNL in kids?

- failed ESWL (most common indication)
- anatomy that would decrease likelihood of ESWL success (most common indication)
 - eg ureteric reimplant, etc
- ablation of calyceal diverticula
- endopyelotomy
- ureterotomy for ureteral strictures

What is involved in the pre-op work-up PNL?

- bowel prep } improves visualization, especially in kids with constipation (neurogenic)
- lab work } CBC, lytes, creatinine, PTT, INR, group & screen
 - } urine C&S
- imaging } pre-op imaging is essential to planning & performance
- ancillary procedures } +/- ureteric catheter (occlusion balloon not usually needed in kids)
 - } Foley
 - } ensure free drainage of urinary stomas
- access } by urologist or by IR
 - fluoroscopic or U/S-guided

How successful is PNL for stone management in kids?

- similar to adults
- post-op imaging to ensure stone-free status is essential

Endopyelotomy

What are the indications for antegrade endopyelotomy in kids?

- not clear because endopyelotomy is not commonly used in kids
- success of open pyeloplasty is very high in kids
- lap pyeloplasty is also better and very minimally invasive
- **main role is likely for failed pyeloplasty**
- ureteroscopic endopyelotomy not good option as kids have small ureter

What are the relative contraindications to endopyelotomy in kids?

- poor renal function
- large collecting system
- long segment of obstruction
- active infection
- ? high inserting ureter
- ? crossing vessel

How successful is endopyelotomy for UPJO in kids?

- hard to estimate given small numbers in literature } ~85% at best

Calyceal Diverticula

What are the indications for intervention in a calyceal diverticulum in kids?

- not common in kids
- infection
- pain
- evidence of symptomatic stones
- hematuria
- progressive renal damage

What is unique about the management of calyceal diverticula in kids?

- **obliteration of neck + scarification of epithelial lining of diverticulum is preferred option**
- dilation of calyceal neck NOT recommended } common option in adults
- } high failure rate & complication rate
- percutaneous approach
- laparoscopic approach

PEDIATRIC LAPAROSCOPY

What are the indications for pediatric laparoscopy?

→ diagnostic

- nonpalpable UDT } presence or absence, location, & anatomy of UDT
- intersex } when gonadal development is abN or discordant with sex of rearing
 - } direct visualization of internal genital organs
 - } diagnostic Bx possible
- hernia } evaluation of contralateral inguinal ring to determine if exploration is req'd
 - can also feel for crepitus in contralateral inguinal canal or scrotum
 - } access through ipsilateral hernia sac after it is opened

→ therapeutic

- intra-abdominal UDT } 1st stage Fowler-Stephens
 - } lap orchidopexy
 - } orchiectomy
- intersex } removal of aberrant gonadal or ductal structures
 - } removal of gonad with risk of malignant degeneration
 - } removal of persistent mullerian ductal structures
- adrenal surgery } CAH, pheochromocytoma
- renal surgery } nephrectomy
 - } partial nephrectomy
 - } renal Bx
- collecting system } lap pyeloplasty
- VUR } lap extravesical ureteric reimplantation
- bladder surgery } lap-assisted bladder reconstruction
 - augmentation
 - catheterizable stoma

What are the patterns that may be seen during laparoscopy for nonpalpable testis?

1) normal

- triangular arrangement of vas, lateral gonadal vessels, and iliac vessels
- obliterated umbilical is seen, vas crosses over towards internal ring
- vessels course into closed ring

2) vanishing testes (16%)

- vas and vessels dwindle away before internal ring
 - no need to explore if vessels not seen } may be necessary to move cecum away

3) vessels pass into ring

- requires inguinal dissection
 - testicular nubbin: 29%
 - testis present: 14%

4) intra-abdominal testis (37%)

- may be "peeping" testis: sits at internal ring

5) nondiagnostic: 3% → various causes

What are the possible findings at diagnostic laparoscopy for intersex conditions?

1) palpable gonads, virilized, possible uterus

- deficiency of MIS } identify and excise mullerian structures

2) no palpable gonads, virilized

- pure gonadal dysgenesis, true hermaphroditism } gonadal bx/removal
 - } define mullerian anatomy

3) asymmetry or 1 palpable gonad, virilized

- MGD } evaluate opposite gonad w/ bx, removal

4) female

- male pseudohermaphroditism, AIS, or 5 α -reductase deficiency } gonadectomy or orchidopexy

What are the contraindications to laparoscopic surgery?

→ ABSOLUTE } } "Bad Reasons CHAMP"

- Bowel obstruction
- Retroperitoneal abscess
- Coagulopathy (uncorrected)
- Hemoperitoneum or hemoretroperitoneum (massive)
- Abdominal wall infection
- Malignant ascites (suspected)
- Peritonitis

→ RELATIVE

- morbid obesity } lap shown to be better for adrenal & renal surgery
 - } less blood loss, less narcotic use, shorter stay, earlier convalescence
 - } complication rate lower for lap sx (~30% vs ~65%)
- extensive prior abdo or pelvic surgery } retroperitoneal approach may be preferred
- prior retroperitoneal surgery } makes re-entering retroperitoneum very difficult
- pelvic fibrosis } previous peritonitis, hip prosthesis, etc
- organomegaly } should consider open Hasson technique
- benign ascites } bowels float closer to anterior peritoneum (watertight closure req'd)
- pregnancy } difficulty increases with larger gravid uterus
 - } access must stay away from fundus of uterus
 - } pneumo and CO₂ may have hemodynamic effects and cause acidosis
- hernia } diaphragmatic hernia may lead to pneumomediastinum
- AAA or iliac aneurysm } Veress needle should be aimed away from aneurysm
 - } consider Hasson or retroperitoneal approach
- severe COPD } hypercarbia may be an issue

What are the main physiologic effects of a pneumoperitoneum?

1) Cardiovascular

- ↓'d CVP if pt has low atrial pressures } ↑'d CVP if pt has high atrial pressures
- ↑'d MAP (hypervolemic), but ↓'d once ≥20mmHg
- ↑'d CO at ~10mmHg but CO ↓'s when ≥20mmHg (decreased venous return)
- ↑'d SVR
- tachycardia (hypercarbia stimulates sympathetics)
- arrhythmias (ventricular extrasystoles from hypercarbia)

→ bradyarrhythmias from vagal stimulation during initiation of pneumo

→ dramatic hypoTN can occur upon insufflation (vaso-vagal response of pneumo)

Rx - desufflate and remove Trendelenburg

2) Respiratory

- ↑'d peak airway pressures
- ↓'d vital capacity due to Trendelenburg and pneumo
- ↓'d FRC
- ↑'d pCO₂

3) Renal

- ↓'d GFR at pressure ≥10 mmHg
- oliguria from ↓'d renal vein blood flow & direct renal parenchymal compression at pressures >10mmHg } use of lasix, mannitol, IVF can decrease oliguria

4) Bowel

- ↓'d mesenteric blood flow } rarely results in mesenteric thrombosis
- less post-op ileus

5) Acid-Base status

- hypercarbia
- respiratory acidosis

6) Hormonal

- less hepatic stress response than open surgery
- less catabolic cytokine and opioid release than open surgery

7) Immunologic

- less immunosuppression than open surgery
- less tumour cell growth after lap surgery

What are the different gas insufflants used to create pneumoperitoneum?

- 1) CO₂ } **not combustible & very soluble in blood (rapid reabsorption)**
 } may cause acidosis and be an issue in pts with severe chronic respiratory disease
- 2) Helium } **inert gas that is not combustible & not an issue for respiratory pts**
 } not very soluble in blood
- 3) Nitric oxide } combustible
- 4) room air

What potential complications are MORE COMMON with pediatric laparoscopic surgery?

→ mostly access-related & pneumoperitoneum-related complications

- 1) pre-peritoneal insufflation } peritoneum more likely to separate from abdominal wall
- 2) pneumoperitoneum issues } kids have ↓'d ability to withstand drops in O₂ saturation
 - kids have higher O₂ consumption
 - pneumoperitoneum significantly reduces FRC
 - more pronounced in neonates
- 2) intra-abdominal organ injury } resistance to penetration is much less and reduced force is needed for injury during access
 - } smaller working space also makes intra-op injury more common
- 3) peritoneal violation w/ retroperitoneal Sx } peritoneum is weaker & more posterior in kids
- 4) port-site hernia } even 5mm ports must be closed in kids
 - } don't need to close 2mm ports
- 5) port-site thermal injury } smaller diameter instruments ↑ risk of electrical capacitative coupling

What is the issue with VP shunts and intra-abdominal laparoscopy?

- there does not seem to be a significant risk
→ with functioning valve, there should be no risk of increased ICP
- no need to exteriorize VP shunt prior to pneumoperitoneum

Renal Surgery

List the advantages & disadvantages of transperitoneal vs retroperitoneal laparoscopic surgery.

	ADVANTAGES	DISADVANTAGES
Transperitoneal	<ul style="list-style-type: none"> - easier - more working space - better for pelvic surgery - good for anterior approach to kidney 	<ul style="list-style-type: none"> - higher risk of intra-peritoneal organ injury - may need more Trendelenburg - previous abdo Sx may preclude
Retroperitoneal	<ul style="list-style-type: none"> - lower risk of bowel injury and post-op ileus - very low risk of trocar site hernia - can avoid hostile abdomen - rapid & direct access to renal hilum - less exposure problems from liver, spleen, or bowel - less risk of contaminating peritoneum from renal pathology (urine, infection, tumour) 	<ul style="list-style-type: none"> - less working space - more pulmonary complications eg pneumothorax

List the advantages & disadvantages of the different retroperitoneal approaches in pediatric laparoscopy?

	ADVANTAGES	DISADVANTAGES
1) prone	<ul style="list-style-type: none"> - kidney falls anteriorly exposing hilar vessels easily - ureter and pelvis are posterior and easily accessed - less chance of peritoneal violation 	<ul style="list-style-type: none"> - smaller working space - would take longer to open in emergencies
2) lateral	<ul style="list-style-type: none"> - greater working space - better access to distal ureter - easier to convert to open in emergencies 	<ul style="list-style-type: none"> - greater chance of peritoneal violation - exposure of hilar vessels not as easy

During nephroureterectomy, how much of the ureter must be removed?

→ depends on pathology } transperitoneal approach likely best

1) VUR + obstruction } entire ureter must be removed

2) free VUR with good drainage } can leave retained stump
 } must tie off ureter with suture to prevent reflux into peritoneum

What is the most common indication for Partial Nx in kids?

- non-functioning renal segment/moiety of a duplex kidney

→ must be careful of the delicate renal vasculature of the remnant segment

→ limit dissection and mobilization of remnant moiety

Bladder Surgery

What are the 3 main forms of laparoscopic bladder reconstructive surgery in kids?

1) lap autoaugmentation

- open detrusor muscle + dissect underlying mucosa

- allows development of large bladder diverticulum

→ improved compliance with low-pressure storage

- post-op bladder drainage needed temporarily due to possibility of bladder rupture

2) lap enterocystoplasty

- requires high degree of laparoscopic skill

3) lap-assisted reconstruction

- eg lap appendicovesicostomy (mitrofanoff)

- harvest & mobilization of tissue for augmentation and/or stoma done laparoscopically

→ upper abdominal access

- reconstruction is done via open lower abdominal incision

→ lower abdominal access

Antireflux surgery

What are the 2 main forms of laparoscopic surgery for VUR?

1) transvesical } not true "laparoscopy"

} percutaneous bladder procedure that uses laparoscopic instruments

} difficult surgery

2) extravesical reimplantation } Lich-Gregoir technique used

→ detrusor incised

→ mucosa exposed

→ ureter placed in trough (new submucosal tunnel)

→ detrusor closed over ureter in trough

Perivesical surgery

What other indications for laparoscopic surgery exist in kids?

- removal of persistent mullerian structures
- excision of SV cysts
- prostatic utricles
- creation of neovagina } sigmoid or ileal vaginoplasty
 } Vecchietti procedure

What is the Vecchietti procedure?

- creation of neovagina } often for Mayer-Rokitansky-Kuster-Hauser syndrome
 → congenital absence of vagina + renal anomalies (absence or ectopia)
- olive-shaped device placed at vaginal dimple
- constant upward traction applied transabdominally via sutures brought out through anterior abdo wall

Chapter #132 – Pediatric GU Trauma

COMPARISION WITH ADULT TRAUMA

What is the cause of pediatric GU trauma?

- **trauma is most common cause of pediatric death**
- blunt trauma accounts for ~90% of GU injuries in kids
 - majority have coexisting injuries to thorax, spine, pelvis/femur, or intra-abdominal organs
- renal trauma accounts for >60% of pediatric GU trauma

Why is the kidney more susceptible to injury in kids?

- weaker protection } pliable rib cage
 - } weaker abdominal muscles
 - } less perirenal fat
- location } sits lower in abdomen
 - controversial whether true incidence of renal injury after blunt trauma is increased in kids

Which renal anomalies are more common in kids undergoing screening CT for trauma?

- 1) UPJO \
- 2) hydroureteronephrosis } 3- to 5-fold more common in kids with trauma
- 3) horseshoe kidney /
- usually have hematuria disproportionate to severity of trauma
- not clear whether associated with higher stage of renal injury

What is the significance of trauma-induced hematuria in kids?

- gross hematuria or micro hematuria + shock associated with identifiable injury in most adults
- in kids, hematuria is very unreliable in determining who to screen for renal injuries
- hematuria (of any degree) may be absent in up to 70% of kids with ≥grade 2 renal injury

What are the indications for imaging of the GU tract after trauma in kids?

→ Santucci et al ('04) showed that criteria is same as adults except for “shock”

- 1) blunt trauma
 - gross hematuria
 - microscopic hematuria (>50 RBCs per HPF) + shock (sBP <90)
 - no hematuria but highly suspicious mechanism of injury (rapid deceleration or high velocity impact) or associated injuries (fractured thoracic ribs, spine, pelvis, or bruising of torso)
- 2) penetrating trauma
 - any degree of hematuria
- 3) pediatric patients with any degree of hematuria

RADIOGRAPHIC & ENDOSCOPIC ASSESSMENT & TREATMENT OF UPPER TRACT GU INJURIES

What is the role of FAST for screening after blunt abdominal trauma?

- Focused Assessment with Sonography for Trauma
- operator and experience dependent
- 70-85% sensitivity
- 93-100% specificity
- FAST will miss 5-10% of clinically significant injuries
- N FAST + N serial P/E over 24hrs virtually rules out presence of significant intra-abdominal injuries

What is the role of a single-shot IVP?

- labile patient taken to OR and unstable for CT
- 2cc/kg iv bolus then image taken at 10-15 mins after injection
 - may still be suboptimal due to poor excretion related to labile hemodynamics
- **main benefit may be to detect normally functioning contralateral kidney**

What is the best study to assess renal injuries?

- triphasic CT abdo/pelvis } precontrast
- } immediately after injection
- } 15-20 minuted delayed film

What are the 2 most likely GU injuries to be missed by a single-shot IVP or a monophasic CT?

- 1) urinomas
- 2) isolated ureteral injuries

What is the grading system for renal trauma?

- AAT
- grade 1 } renal contusion or subcapsular hematoma (nonexpanding)
- grade 2 } nonexpanding perirenal hematoma (confined to retroperitoneum) OR laceration (<1cm)
- grade 3 } laceration >1cm WITHOUT violation of collecting system or urinary extravasation
- grade 4 } laceration into collecting system OR main renal artery or vein injury w/ contained hemorrhage (including segmental artery or vein)
- grade 5 } shattered kidney OR avulsion of renal hilum (devascularized kidney)
- *** advance one grade for bilateral injuries, up to grade 3 ***

How common is secondary/delayed hemorrhage after renal trauma?

- occurs in ~25% of patients with grade 3-4 renal trauma managed in non-operative fashion
- usually develops 10-14 days after injury
- usually due to development of AVF or pseudoaneurysm
 - **unlike AVFs that develop after renal Bx, most AVFs after trauma need Rx**
- Rx → selective angiographic embolization } ~80% success rate
- } decreased risk of renal loss cf open exploration
- open exploration } ONLY for failed embolization

What is post-embolization syndrome?

- self-limited condition } usually resolves within 3-4 days
- fever + flank pain + ileus
 - need to r/o fever is from infection of necrotic renal tissue
- less common after trauma (10%) than after embolization of renal tumours (60%)

What are the indications for retrograde pyelography after renal trauma?

- 1) to r/o a partial or total ureteric disruption
 - either no initial imaging or only monophasic CT due to labile patient
 - delayed-phase CT 2-5 days after trauma may not be conclusive or diagnostic
ie may only see perirenal or upper ureteric extravasation with no visualization of distal ureter
- 2) to aid in management of symptomatic urinoma
 - most post-trauma urinomas are asymptomatic and most resolve with conservative management (85%)
 - occasionally can persist and be associated w/ continued flank pain, ileus, and/or fever
 - **ureteral stent just as effective as perc NT**

What are the indications for f/u renal imaging after pediatric renal trauma?

- not recommended for grade 1 and 2 renal injuries
- not recommended for grade 3 renal injuries with all fragments viable
- repeat CT + delayed images recommended at 2-3 days post-trauma for all other injuries
 - **grade 3 with devitalized fragments, grade 4, and salvaged grade 5 renal injuries**
 - r/a the hematoma/urinoma
 - **3 month f/u triphasic CT also recommended**
- also recommended for all patients with persistent (>72hrs) and/or increased fever, flank pain, gross hematuria, regardless of degree of injury

What are the indications for DMSA renal scan after renal trauma?

- **DMSA scan any time >1 week after trauma gives valid prognosis of renal function**
 - almost no recovery of function seen >1 week after injury
- 1) grade 3 renal injury + devitalized fragments
- 2) grade 4 injuries
- 3) grade 5 injuries
- 4) persistent HTN

MANAGEMENT OF RENAL TRAUMA

What are the 3 main schools of thought regarding renal exploration after trauma?

- 1) regardless of mechanism of injury, as long as there are no absolute indications for exploration, **ALL RENAL TRAUMA CAN BE OBSERVED**
- 2) renal exploration + renorrhaphy should be performed for all grade 3 or higher renal injuries
IF A LAPAROTOMY IS PERFORMED for co-existing intra-abdominal injuries
 - controversy regarding the need to obtain renal hilar control before renal exploration
 - some studies showed no difference in Nx rate
- 3) despite laparotomy for co-existing intra-abdominal injuries, no renal exploration needed if trauma surgeon can **SEPARATE ENTERIC INJURY FROM GU TRACT WITH OMENTUM** (or other alternative tissue) + **PLACE DRAINS**
 - separation will prevent breakdown of enteric repairs due to urine leaks and will keep enteric bacteria away from GU tract

What are the consensus recommendations for management of renal trauma in kids (CHART)?

→ based on hemodynamic stability, accurate imaging to stage injury, & presence of associated organ injury

CLINICAL FINDINGS/GRADE OF INJURY	RECOMMENDED TREATMENT
- grade 1 or 2 renal injuries	non-operative
- isolated grade 3, 4 & stable grade 5	non-operative
- instability or uncontrollable renal hemorrhage	absolute indication for Sx
- persistent or delayed hemorrhage not responding to embolization	absolute indication for Sx
- expanding pulsatile mass found on surgical exploration for co-existing abdo injuries	absolute indication for Sx (verify contralateral kidney)
- inadequate pre-op radiographic staging due to instability + retroperitoneal hemorrhage found on exploration	exploration recommended (verify contralateral kidney)
- grade 3 injury with devitalized fragments, grade 4, or grade 5 renal injuries + co-existing intra-abdominal injuries (esp duodenum, pancreas, colon)	exploration + renorrhaphy and repair recommended

What is involved in non-operative therapy for renal trauma in kids?

- bed rest
- serial monitoring of vitals, urine output, abdominal exam, and CBC } blood transfusions PRN
- Abx as indicated
- repeat CT scan in 2-3 days } recommended for grade 3 + devitalized fragments, grade 4, & grade 5
- embolization for continued bleeding and/or if patient becomes unstable
- consider ureteric stent or perc NT if urinoma w/ increasing/persistent flank pain, ileus, low-grade fever
- ambulation once gross hematuria resolves
- no strenuous activity for 6 weeks

What are the indications for ABx in renal trauma?

- 1) penetrating trauma
- 2) blunt trauma with large retroperitoneal hematoma
- 3) blunt trauma with urinary extravasation

How successful is non-operative management of renal trauma?

- a) grade 1 & 2 renal injuries
 - minimal GU complications
- b) isolated grade 3 to 4 renal injuries
 - up to 50% will need embolization, endoscopic or percutaneous intervention
 - ~25% will need intervention for persistent or delayed bleeding
 - ~25% will need intervention for symptomatic urinomas
 - open surgical exploration will be required in 5%

What are the indications for renal exploration?

→ absolute

- hemodynamic instability due to renal source
- expanding or pulsatile retroperitoneal hematoma
- inability to stop persistent or delayed bleeding via embolization

→ relative

- co-existing intra-abdominal injury needing laparotomy + grade 3 or higher renal injury
- retroperitoneal hematoma found at time of laparotomy in patient with incomplete pre-op imaging to stage kidney injury
- urinary extravasation or nonviable tissue
 - high complication rate if >20% nonviable tissue + parenchymal laceration + urinoma
- delayed Dx of arterial injury
- arterial injury in solitary kidney or bilateral arterial injury

What are the main principles of renal salvage after exploration?

→ **early vascular/hilar control before exploration is CONTROVERSIAL**

- complete exposure of injured kidney
- debridement of nonviable tissue
- suture ligation of bleeding arterial vessels
- watertight repair of collecting system injuries } consider stent or perc NT if major injury or defect
- coverage or approximation of parenchymal defect

What are the indications for Nx after renal trauma?

→ sometimes patient is too unstable to attempt renal reconstruction

→ damage control (packing off area) is an option

- 1) extensive renal injury threatening life
- 2) extensive renal injury with non-salvageable kidney

RENAL VASCULAR INJURIES

What is the recommended management of renal arterial injuries?

- 1) main renal artery } **Nx preferred (salvage rate very low)**

→ hemodynamic instability, inadequate collateral blood flow, and warm ischemic time invariably results in low salvage rate

} reconstruction only in select cases (eg solitary kidney)

} endovascular repair also an option but anticoagulation is an issue

- 2) segmental renal artery } observation
- } Nx if indicated

What are the indications for renal arterial reconstruction?

- 1) hemodynamically stable patient + injury to solitary kidney
- 2) hemodynamically stable patient + bilateral renal arterial injuries
- 3) incomplete arterial injury + perfusion maintained (partially occluded artery or collateral vessels)

What is the recommended management of renal venous injuries?

- usually a venous tear requires closure with 5-0 prolene
- if small laceration or thrombosis, can try conservative non-operative mgt
- segmental venous injuries best managed by ligation (collateral venous drainage)

TRAUMA-INDUCED RENAL VASCULAR HYPERTENSION

What are the common causes of post-traumatic renal HTN?

→ persistent HTN >30 days after injury could be due to renal source so should be investigated

→ **5% incidence of traumatically induced HTN after grade 3 or higher renal injury**

→ usually develops within 3 yrs after injury

- 1) renal ischemia from segmental arterial occlusion
- 2) main renal artery occlusion with intact peripheral flow to the kidney
- 3) traumatically induced AVM
- 4) Page kidney

What are the recommended investigations to assess possible post-traumatic renal HTN?

- DMSA scan } differential function
- CT angiography or MRI } to rule out AVM
- renal vein renin sampling } if surgical intervention is considered

What is the most common clinical finding in post-traumatic HTN?

- small poorly functioning kidney (<20%) + pan-nephric scarring

What are the management options for post-traumatic renal HTN?

- depends on the cause
- AVM } embolization
- renal ischemia } partial nephrectomy
- } Nx
- if solitary kidney } vascular reconstruction (+/- grafting)

UPJ DISRUPTION

How does UPJ disruption present after trauma?

- diagnosis is often delayed for >36hrs in >50%
 - often Dx'd during w/u for persistent post-op fever, chronic flank pain, continued ileus, sepsis
- most commonly caused by rapid deceleration injuries or by a sudden extreme hyperextension
 - mobile kidney with relatively fixed ureter
- vascular instability
- hematuria in 70%
 - 30% have no hematuria
- usually associated with other life-threatening injuries
 - diagnosis often missed on initial assessment (pt often too unstable for imaging)
 - laparotomy often fails to reveal retroperitoneal hematoma

Are traumatic UPJ disruptions more common in kids with hydronephrosis or congenital UPJO?

- likely NO
 - these kids tend to get major laceration through thinned renal cortex (grade 3 injury) or laceration of renal pelvis
 - Rx → retrograde pyelogram to confirm UPJ is normal
 - stent or perc NT

What are the 3 classic findings on triphasic CT that are associated with UPJ disruption?

- 1) good renal contrast excretion + medial extravasation in perirenal & upper ureteral area
- 2) absence of parenchymal lacerations
- 3) no visualization of ipsilateral distal ureter

What is the management of UPJ disruption?

- **if Dx made within 5 days of trauma } immediate repair if patient is stable**
 - debridement, spatulation, reanastomosis, stent + NT, and retroperitoneal drain
 - } urinary diversion if unstable
- delayed diagnosis of ≥6 days } percutaneous NT + delayed reassessment
 - } at 12 wks, DMSA renal scan to assess function + antegrade/retrograde studies to assess length of injury
 - primary UU
 - ileal ureter
 - auto-Tx
 - Nx

URETERAL TRAUMA

How common are ureteral injuries after external trauma?

- relatively uncommon
- <4% of penetrating trauma
- few reports after blunt trauma
- 10% coexist with renal or bladder injuries
- 90% associated with other intraperitoneal organ injuries
- mortality rate associated with ureteral injury is >30%

How do ureteral injuries present?

- no hematuria in up to 67%
- diagnosis usually made on triphasic CT
- may get delayed presentation, particularly with high velocity GSWs
 - blast injury + missile tumbling can result in extensive damage to surrounding tissues that presents as delayed necrosis
 - may see increased drainage output 3-5 days after the injury
- pediatric iatrogenic ureteric injuries are uncommon relative to adults

What is the management of ureteral injuries?

→ **depends on extent, location, and mechanism of injury**

- 1) ureteral perforation after ureteroscopy } stenting +/- NT placement
 - } removal of stent after 6-8 weeks
 - } U/S 4-6 weeks after stent removal
 - } good long-term results
- 2) ureteral contusions or inadvertent ligation } removal of clip or ligature
 - } stent for 6-8 weeks
 - } U/S 4-6 weeks after stent removal
 - } long-term imaging necessary to r/o strictures
- 3) traumatic ureteral injury Dx'd within 5 days } immediate surgical repair preferred
 - ureteral anastomosis to pelvis
 - primary UU
 - TUU
 - ureterocalicostomy
 - ureteral reimplantation
 - Psoas Hitch
 - Boari flap
 - ileal ureter
 - auto-Tx
 - Nx
 - } if unstable, can tie off ureter and place NT then repair at a later date (3 months)
- 4) traumatic ureteral injury Dx'd ≥6days later } NT +/- ureteral stent
 - } repair at a later date (3 months)

BLADDER INJURIES

What are the indications for bladder imaging after blunt trauma?

- absolute
 - 1) gross hematuria + pelvic fracture
 - 2) inability to void
 - 3) penetrating trauma near midline pelvis
- relative
 - 1) urinary clot retention
 - 2) perineal hematoma
 - 3) hx of prior bladder augmentation

What imaging techniques are used to assess bladder injuries?

- standard or CT cystogram
- must instill enough contrast } at least 1/2 estimated bladder capacity [(age +2) x 30cc]

What is the management of bladder injuries in kids?

- extraperitoneal injuries 2x more common than intraperitoneal injuries
- extraperitoneal bladder injuries are almost invariably associated with pelvic fracture
- 1) extraperitoneal bladder injuries
 - iv Abx
 - urethral catheter drainage x 7-10 days
 - S/P tube if too young for large urethral catheter
 - cystogram prior to removal of catheter
 - open repair if evidence of bony spicule protruding into bladder or evidence of BN laceration
- 2) intraperitoneal bladder injuries
 - open repair recommended for all cases
 - perivesical drain
 - large urethral catheter x 7-10 days
 - S/P tube if too young for large urethral catheter
 - cystogram prior to removal of catheter

What is the management of BN injuries in kids?

- **traumatic bladder lacerations in kids are 2x more likely to extend through the BN**
- anterior BN lacerations often associated with urethral injuries
- 1) **open surgical exploration with intravesical repair**
 - better short term & long term outcomes
 - don't dislodge pelvic hematoma to help prevent blood loss
 - after repair, VCUG at time of catheter removal to confirm healing
- 2) S/P tube +/- urethral catheter
 - more likely to develop persistent urinary extravasation, pelvic urinoma/abscess, or pelvic osteomyelitis
 - increased risk of long-term urinary incontinence

URETHRAL INJURIES

What are the main differences between kids & adults with respect to posterior urethral injuries?

- pelvis is immature & bladder is relatively intra-abdominal in comparison to adults
- 1) pelvic # more likely to be unstable & assoc'd with severely & permanently displaced prostatic urethra
 - more likely to need transpubic, trans-symphyseal, or combined transpubic and perineal dissection for urethral repair
- 2) complete posterior urethral disruption more common due to severe displacement of prostate off the pelvic floor
 - ED will be more common
- 3) concurrent bladder & urethral injuries may occur in up to 20% and longitudinal tears through BN/sphincter is 2x more common
 - higher risk of permanent urinary incontinence
- 4) in prepubertal girls, pelvic #s are 4x more likely to be assoc'd w/ urethral injuries than in adult women
 - higher risk of permanent urinary incontinence

What are the indications to evaluate for urethral injury in kids?

- usually there is a hx of direct trauma to penis, vagina, perineum, or pelvis
- 1) classic triad of perineal/penile hematoma + blood at meatus/introitus + inability to void
- 2) if ≥1 pubic rami are fractures or symphyseal diastases are present
 - urethral injury rare after isolated fracture of acetabulum, ilium, or sacrum
- 3) imaging suggests a BN injury

What are the initial investigations used to assess and diagnose a urethral injury?

- static cystogram } can assess bladder and BN
 - } perform VCUG + RUG + VUDS if BN injury suspected
- RUG } male urethra
 - } can delineate characteristics of urethral injury
- cystourethroscopy + vaginoscopy } female urethra or males with BN injury
- DRE } mandatory for all pelvic #'s with urethral injury
 - **can detect occult rectal injury**
 - } concurrent rectal injury found in ~15% of PFUDs assoc'd w/ pelvic fractures

What is the management of anterior urethral injuries?

- usually iatrogenic
- 1) urethral instrumentation
 - Rx → establish urethral continuity } S/P tube if unable
 - ABx
 - f/u VCUG at 1-3 wks
 - if normal, repeat RUG 3 months later (uroflow + PVR if toilet trained)
- 2) Cx associated with 3 types of urethral injuries
 - a) meatal injury
 - Rx → meatoplasty
 - b) loss of distal urethra secondary to partial or complete glanular amputation
 - Rx → reanastomosis of urethra + glans with stenting
 - Abx
 - compressive dressing to immobilize glans
 - c) development of UC fistula due to ischemia
 - Rx → similar to post-hypospadias repair
 - delayed until 6-9 months of age
- 3) during repair of anorectal malformations
 - usually due to lack of urethral catheter at time of repair or if catheter goes into rectum via urethrorectal fistula
 - usually get proximal penile or bulbar urethral injury (excised or partially avulsed)
 - repair much easier with better outcomes if catheter was in place at time of injury

What is the initial treatment of posterior urethral injuries in kids?

- broad-spectrum ABx } prevent bacterial contamination of pelvic/perineal hematoma & extravasated urine
- assess competency of BN
- establish urinary drainage } urethral catheter (primary realignment), S/P tube, vesicostomy
- decide timing of repair } early (primary realignment or sutured end-to-end)
 - } late (any type of repair occurring ≥ 3 months after injury)
 - after initial urinary drainage, if permanent urethral stricture develops, usually wait until >1yr of age or at least 3months after injury

What investigations are used to assess urethral strictures before delayed repair?

- RUG } to identify location of stricture
- VCUG } performed if BN is N
- cystogram } if contrast in posterior urethra, need to do VUDS
 - to determine BN injury vs poor bladder contraction
- cystourethroscopy } if evidence of, or suspicion of, BN injury
- pelvic MRI } can delineate degree of PFUD
 - can't assess BN competency

What are the management options for delayed urethral repair?

- 1) endoscopic
 - primary endoscopic realignment
 - **not as beneficial as in adults, especially after trauma (ie PFUD)**
 - good option for iatrogenic partial injuries
 - VIU
 - good short term results but long-term results not as good (20-35%)
 - >1 VIUs not recommended due to poor outcomes & deleterious effect on future open urethroplasty procedures
 - cut-to-light
 - poor results and not recommended
- 2) open urethroplasty
 - complete excision of scar tissue
 - wide spatulation
 - tension-free
 - **perineal, transpubic, trans-symphiseal, or combined approach**
 - excellent outcomes (90%)
 - treatment of choice for PFUD
 - end-to-end technique or patch urethroplasty (flap vs graft ... one-stage vs staged)
 - if 2-3 cm defect, end-to-end preferred
 - penile or preputial flap (Orandi)
 - free skin graft or buccal mucosal graft

What are the techniques to gain more urethral length for open urethroplasty?

- 1) mobilization of spongiosum off cavernosal bodies
- 2) separation of corporal bodies
- 3) inferior pubectomy
- 4) corporal rerouting

What are the indications for combined abdominoperineal approach (with or without partial pubectomy)?

- 1) severe fibrosis
- 2) previous failed anastomotic urethroplasty
- 3) associated BN injury
- 4) **kids**

What are the 2 main options for kids with combined BN and urethral injuries?

- 1) **continent catheterizable stoma (Mitrofanoff) w/ no attempt to reestablish urethral continuity**
→ likely better outcomes with less morbidity
- 2) BN reconstruction + urethroplasty
→ usually get persistent urinary incontinence
→ **usually requires subsequent AUS or BN sling } high complication rate**

What is the incidence of ED post urethral injury?

- ED rates not increased with primary realignment or primary reanastomosis
→ result of severity of primary injury NOT initial treatment modality
- ED rate higher if total disruption of urethra or if prostate is grossly dislocated (~70% vs 30%)
→ both are **more common in kids**

What is the cause of urinary incontinence after urethral injuries?

- due to concurrent BN and urethral injury
- denervation of sphincteric complex due to pelvic or pudendal nerve damage also plays a role
→ directly related to severity of primary injury NOT result of initial treatment modality

What is the management of female urethral injuries in kids?

- **almost always associated with an unstable pelvic fracture**
- usually caused by a) disruption of pubic symphysis with longitudinal laceration through BN & urethra
or b) dislocation of bony fragment that lacerates urethra
- **75% associated with concurrent vaginal laceration**
- **30% associated with concurrent rectal injury**
- 1) avulsion distraction injuries } immediate end-to-end urethroplasty
- 2) BN/urethral injuries } primary BN repair + repair of longitudinal laceration over urethral catheter
→ diversion + delayed repair is less successful & has more complications
- 3) concurrent vaginal injury } concurrent repair
- 4) concurrent rectal injury } diverting colostomy

PENILE INJURIES

What is the management of penile injuries?

→ most commonly iatrogenic (eg post-Cx)

- 1) excess penile skin removal during Cx } wet-to-dry dressings + Abx ointment
→ healing by 2° intention
→ skin grafting results in poor cosmesis
} if totally degloved, can salvage penile shaft skin, defat, and replace as FTSG
- 2) penile strangulation by FB } removal ASAP
→ delayed presentation can lead to significant damage to NVB, corporeal bodies, and urethra
} consider CAS investigation
- 3) animal bites } most severe form of penile trauma in kids
} tetanus vaccination
} check animal for rabies
} liberal use of Abx, wound cleansing, debridement, and repair or reattachment

SCROTAL/VULVAR AND TESTICULAR TRAUMA

What are the classifications of scrotal or vulvar trauma?

→ result of sports, an assault, or a fall

1) penetrating trauma

→ need to r/o injuries to urethra & rectum } rectal exam, urethroscopy, etc

→ Abx, cleansing & debridement, tetanus immunization

2) blunt trauma

→ usually self-limiting

What are the indications for scrotal exploration after trauma?

- evidence of a hematocele

- evidence of rupture of tunica albuginea

- evidence of intratesticular hematoma

→ delay in diagnosis and/or treatment of testicular injury of >72 hrs can result in a 3-4fold increased risk of testicular loss

Rx → removal & drainage of scrotal hematoma

→ excision of necrotic tissue

→ reapproximation of tunica albuginea

Ethics, CanMEDs, Statistics, etc

ETHICS

List the 3 main components of valid consent. }} “DVC”

- “Disclosure” } risks & benefits
- “Voluntary” } without duress
- “Capacity” } competency
- maybe “Related to treatment” (CPSO)
- maybe “Non-coerced” is separate element (CPSO)
- underlying principle is autonomy & respect for persons

List the 4 principles of medical ethics

- Autonomy (likely most important)
- Non-maleficence
- Beneficence
- Justice

Conditions that allow surgeon to refuse patients/family’s requests.

- futile
- harmful to patient
- harmful to others
- patient incapacitated

CanMEDs

List the 7 CanMEDS 2005 Physician Roles. }} MC SPACE

- 1) **M**anager
- 2) **C**ollaborator
- 3) **S**cholar
- 4) **P**rofessional
- 5) **A**dvocate (Health)
- 6) **C**ommunicator
- 7) **E**xpert in medicine

RESEARCH / STATISTICS

List criteria for an effective screening tool.

→ the disease

- disease is highly prevalent or highly lethal
- natural history of disease is understood
- can detect disease at early stage
- there is a more effective treatment for disease at earlier stage
- early detection of disease improves outcomes

→ the test

- good sensitivity
- cost effective
- non-invasive
- easy to perform/administer
- acceptable test

Define sensitivity

- sensitive test allows you to rule out a Dx } “SNOUT”
- highly sensitive test has low false negatives
- $TP / TP + FN$

Define Specificity

- specific test allows you to rule in a Dx } “SPIN”
- highly specific test has low false positives
- $TN / TN + FP$

What is a type 1 error?

→ **α error**

- when one rejects the null hypothesis when it is actually true
 - probability of assuming a relationship exists, when it actually doesn't
- **p-value**

What is a type 2 error?

→ **β error**

- when one fails to reject the null hypothesis
 - probability of assuming a relationship doesn't exist, when it actually does
- affected by **power** of study

What is lead time bias?

- early diagnosis doesn't change natural history of disease, but falsely appears to prolong survival

What is length time bias?

- screening test will be more likely to detect more indolent disease because those with aggressive disease are dying between screening intervals

What is attribution bias?

- physicians are more likely to attribute COD to a known malignancy even if it is not related

<i>Levels of Evidence</i>
Level 1: Systematic reviews, meta-analyses, good-quality randomized controlled clinical trials
Level 2: Randomized controlled clinical trials, good-quality prospective cohort studies
Level 3: Case-control studies, case series
Level 4: Expert opinion
<i>Grades of Recommendation</i>
Grade A: Based on level 1 evidence (highly recommended)
Grade B: Consistent level 2 or 3 evidence (recommended)
Grade C: Level 4 studies or "majority evidence" (optional)
Grade D: Evidence inconsistent or inconclusive (no recommendation possible)

What are the different study designs used?

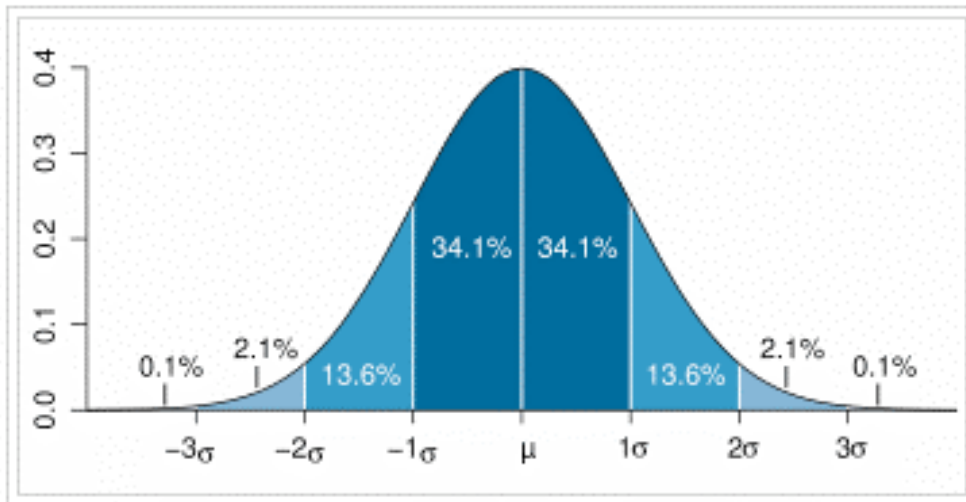
- experimental studies
 - 1) RCT
- observational studies
 - 2) cohort (prospective vs retrospective) } defined group followed ... outcomes compared based on exposures, etc
 - 3) case-control (usually retrospective) } group with disease/outcome ... compared to control group without disease/outcome
 - 4) cross sectional studies
 - 5) case series

What are the categories used for drug safety recommendations?

Class A	- safest - well-designed HUMAN studies have shown NO RISK to fetus
Class B	- safe - well-designed ANIMAL studies have shown NO RISK to fetus, but no good human trials OR - animal studies show a risk to fetus, but well-designed HUMAN studies show NO RISK
Class C	- caution - NO STUDIES in animals or humans OR - ANIMAL studies show HARM to fetus, but NO INFO on affects on HUMANS
Class D	- definite risk - HUMAN studies show RISK to fetus, but benefits may outweigh risks in certain situations
Class E	- definite harm - HUMAN studies show HARM to fetus, and this can't be outweighed by any benefit

What are the 3 phases of a clinical trial?

- phase 1 } define a dose and schedule
- phase 2 } seek evidence of a biologic or antitumour effect
- phase 3 } establish efficacy & safety compared to an established standard of care or placebo



→ STANDARD DISTRIBUTION } 1 SD = 68%
 } 2 SDs = 95%
 } 3 SDs = 99.7%

List advantages & disadvantages of a meta-analysis

→ advantages

- generalizability to population of studies
- ability to control for between study variation
- higher statistical power to detect an effect
- deriving & statistical testing of overall factors/effect size

→ disadvantages

- sources of bias are not controlled (garbage in ... garbage out)
- reliance on published studies (publication bias)
- pooling of heterogenous studies
- language bias
- selection of study bias

Table 87-15 -- Inherent Weaknesses of Meta-Analyses

Pooled results incorporate biases of individual studies
New sources of biases created
Selection of studies
Publication bias (only positive trials usually published)
Language bias
Heterogeneity of the studies
Inclusion/exclusion criteria
Study designs
Assessments of efficacy
Variable placebo response rates
Study duration

Urology Mnemonics (rated R)

ANATOMY

Nerves of the Lumbar plexus

→ “GOLF”

- Genitofemoral nerve (L1-L2)
- Obturator nerve (L2-L4)
- Lateral cutaneous nerve of thigh (L2-L3)
- Femoral nerve (L2-L4)

Muscles that insert into the perineal body

→ “TREBLE”

- Transverse perineii (superficial & deep)
- Rectourethralis
- EUS
- Bulbospongiosus
- Levator ani
- External anal sphincter

Fascia that insert into the perineal body

→ “Perineal DEC”

- Perineal membrane
- Denonvillier’s fascia
- Endopelvic fascia
- Colles’ fascia

Branches of the internal iliac artery

- POSTERIOR branch (3) } } } “pALS”

- 1) Ascending lumbar
- 2) Lateral sacral
- 3) Superior gluteal

- ANTERIOR branch (8) } } } “OSIOMUII”

- 1) Obliterated umbilical
- 2) Superior vesical
- 3) Inferior vesical
- 4) Obturator
- 5) Middle rectal
- 6) Uterine
- 7) Inferior gluteal
- 8) Internal pudendal (terminal branch)

Branches of the internal pudendal artery.

→ “IPP BP, CP”

- inferior rectal
- posterior scrotal/labial
- perineal
- artery to Bulb of Penis
- common penile } dorsal, cavernosal, bulbourethral

LAPAROSCOPY

List contraindications to laparoscopic surgery

→ “Bad Reasons CHAMP”

- Bowel obstruction
- Retroperitoneal abscess
- Coagulopathy (uncorrected)
- Hemoperitoneum, hemoretroperitoneum
- Abdo wall infection
- Malignant ascites suspected
- Peritonitis

List complications of CO₂ pneumoperitoneum at standard 15 cm H₂O

→ “MR CHAOS BP”

- Mesenteric ischemia
- Respiratory acidosis
- CO₂ embolus
- Hypercapnia
- Arrhythmias
- Oliguria
- Subcutaneous emphysema
- Barotrauma
- Pneumothorax, pneumomediastinum, pneumopericardium

IMAGING

RFs for contrast nephropathy

→ “RADD Nephrotoxic CHAMP”

- Renal insufficiency (most predictive)
- Age >65
- DM } must hold metformin x 48hrs (risk of lactic acidosis if renal failure occurs)
- Dehydration
- concurrent Nephrotoxic drugs (eg ACE inhibitors, cyclosporine, NSAIDs, etc)
- CHF
- HTN
- Amount of contrast used (high) or recent contrast use
- Multiple myeloma/ hyperuricemia
- Proteinuria

RFs for idiosyncratic reaction to contrast dye

→ “SHAAP”

- 1) Shellfish allergy
- 2) High-osmolar contrast used
- 3) Asthma
- 4) Atopy (hay fever, food allergies, etc)
- 5) Previous reaction (risk of subsequent reaction is 3-4x greater)

Causes of cortical nephrocalcinosis

→ “CORTICAL”

- Cortical necrosis
- Oxalosis (primary)
- Rejection of Tx
- Toxins (ethylene glycol, etc)
- Insufficient Vit B6 (pyridoxine)
- Chronic GN
- Alport's
- sickle cell

DDx of a filling defect on retrograde pyelogram.

→ “U CANT See Filling Problem”

- Ureteritis cystica
- Clot
- Air bubble
- Necrotic papilla
- Tumour
- Stone (radiolucent)
- Fungus ball
- Polyp

BPH**List the 7 questions of the AUA symptom score.**

→ “FUNWISE” } in last 1 month

- | | | |
|--------------------|-------|----------|
| - Frequency | | |
| - Urgency | 0-7 | mild |
| - Nocturia | 8-19 | moderate |
| - Weak stream | 20-35 | severe |
| - Intermittency | | |
| - Straining | | |
| - Emptying problem | | |

Factors that contribute to development of BPH

→ “FAE SIGN”

- Family history
- Androgens
- Estrogens
- Stromal-epithelial interactions
- Inflammation
- Growth factors
- Neurotransmitters

CUA Guidelines for investigating male LUTS

→ “HUPA DUCS”

- mandatory } History & Physical
- } Urinalysis
- recommended } PSA
- } AUA symptom score
- optional } Diary
- } Uroflow & PVR
- } Creatinine
- } Sexual inventory (eg IIEF)

Absolute indications for surgical management of BPH

→ “SHITRR”

- Stones (recurrent)
- Hematuria (recurrent)
- Infections (recurrent)
- Therapeutic failure of meds \
- Retention (failed TOV) } only absolutes as per CUA Guidelines
- Renal insufficiency /

Indications for cysto in men with LUTs

→ “CHUCS”

- CIS suspected
- Hematuria
- Urethral strictures
- Cancer (bladder)
- Surgery prior (for LUTs)

Indications for upper tract imaging in men with LUTs

→ “SHIRS”

- Stone
- Hematuria
- Infections (UTIs)
- Renal insufficiency
- Surgery prior (GU tract)

Indications for open prostatectomy over TURP

→ “75 LUSH Treatments”

- gland >75g
- Lithotomy issues (hip issues, etc)
- Urethral issues (complex strictures, etc)
- Stone too large for transurethral fragmentation
- Hernia that needs concomitant repair
- Tic in bladder that needs concomitant repair

INCONTINENCE & VOIDING DYSFUNCTION

Indications for UDS

→ “CRRYPT My Neurogenic Bladder”

- Combined storage & voiding symptoms
- Refractory to presumed appropriate Rx
- Recurrent incontinence after previous surgery
- Young male with LUTs
- Paeds (“DDD”) } daytime urgency, diurnal enuresis persists, dysraphism
- Therapy with significant side effects planned
- Mixed incontinence (SUI + urgency)
- Neurologic disease
- BOO

Indications for Video UDS

→ “I ♥ PORNO”

- Incontinence
- Post-op
- Obstruction
- Reflux
- Neurogenic bladder
- Other anatomic abnormalities (tics, fistulae, etc)

Different types of pressure transducers used for UDS

→ “RICO”

- Resistive
- Inductive
- Capacitive
- Optoelectronic

Diseases associated with bladder areflexia

→ “SIDS MD”

- Sacral SCI
- Iatrogenic injury (eg APR, etc)
- DM
- Spina Bifida
- MS (20-40%)
- DDD

Diseases associated with poor compliance

→ “SIMS”

- Sacral SCI
- Iatrogenic injury (eg APR, etc)
- MSA (eg Shy Drager)
- Spina Bifida

Diseases associated with DESD

→ “SMCS-T”

- Suprasacral SCI
- MS (30-65%)
- CP (25%)
- Spina bifida (10%)
- Transverse myelitis

Features that help differentiate MSA (eg Shy-Drager) from Parkinson’s disease?

→ “SPICES worse with TURP”

- Symptoms } LUTs often present before Dx of MSA
- PVR } high residuals with MSA
- Incontinence } much more common with MSA
- Compliance issues } bad compliance in MSA
- ED } often present before Dx of MSA
- Sphincter } denervated in MSA (open & smooth) cf pseudodysynergia in PD
- Worse after TURP } symptoms worse in MSA

Causes of tethered cord

→ “Scar Fixed To Bone”

- Scar from prior surgery
- Fibrous or fibroadipose Filum terminale
- Tumour
- Bony septum

Indications for sphincterotomy

→ “A DUCHI”

- Autonomic dysreflexia from DSD
- DESD
- Upper tract deterioration risk in high risk patients (DLPP >40 cm H₂O)
- CIC difficulties
- High pressure voiding with severe hydronephrosis or VUR
- Independence of patient

Contraindications to Botulinum toxin injections

→ “BLAME Poison”

- Breastfeeding
- Lou Gherig’s disease (ALS)
- Aminoglycoside use
- Myasthenia gravis
- Eaton-Lambert syndrome
- Pregnancy

Contraindications to use of urethral stent (eg UroLume)

→ “Can’t Put Past PUSSY”

- Cancer (urethral)
- Prostatic stent } can’t have both prostatic and urethral
- Perineal urethrostomy
- Pendulous urethral strictures } penile or meatal
- UTI (active)
- Skin graft used for prior urethral reconstruction
- Strictures associated with deep Spongiofibrosis } ie PFUD
- Young patients (relative)

Causes of transient incontinence

→ “DIAPPERS”

- Delirium
- Infection (symptomatic UTI)
- Atrophic vaginitis/urethritis
- Psychological (depression, neurosis)
- Pharmacologic (meds)
- Excess urine production
- Restricted mobility
- Stool impaction

Contraindications to Neurostimulation

→ “Trade Magdy PEPSI For Neurostim”

- Tumour of SC
- Myogenic damage (acontractility)
- Peripheral nerve injury
- End-stage, contracted bladder
- Pregnancy
- Sacral SCI
- Incapacitated patient (eg mental retardation)
- Functional incontinence
- Non-compliant patient

Contraindications to anti-muscarinics

→ “GO CHUG MILK”

- | | |
|-----------------------------|----------------------|
| - Glaucoma (narrow angle) | - Myasthenia gravis |
| - Obstructed bowel | - Impaired cognition |
| - Cardiac disease + HTN | - Liver disease |
| - HyperT4 | - Kidney disease |
| - Urinary obstruction (BOO) | |
| - GERD | |

Medications that help decrease outlet resistance

→ “AID 4 Bladder”

- Alpha blockers
- Isosorbide dinitrate (NO donor)
- Dantrolene
- Botox
- Baclofen
- Benzodiazepines
- α -Bungaratoxin

RFs for urethral erosion of a TVT

→ “Dissect CUTTER ”

- Dissection too close to urethra (devascularization)
- Catheterization/dilation (traumatic)
- Urethral injury at time of insertion (iatrogenic)
- Tension (excessive)
- Twisting of tape
- Estrogen deficiency (eg older age)
- Radiation

Contraindications to placement of an AUS

→ Absolute } “Very Difficult, SID Called Herschorn’s Office”

- VUR at low pressures
- DESD
- Strictures (unstable)
- Infections (skin, urine)
- Dexterity issues (unable to operate device)
- Compliance issues
- High pressure voiding/contractions (≥ 40 cmH₂O)
- Overactivity at low volumes

→ Relative } “STACI”

- Stones (may need repeat cysto)
- Tissue quality poor
- Anatomic abnormalities (eg urethral tic)
- Cancer (need repeat cysto)
- Immunosuppression (steroids, DM, etc)

Causes of persistent fistulae

→ “FRIENDO”

- FB
- RADs
- Infection/ischemia
- Epithelialization
- Neoplasm
- Distal Obstruction

RFs for development of VVF after TAH

→ general } “DIAPRS”

→ specific } “Make New Cunt PEE”

- | | |
|-------------------|--------------------------------------|
| - DM | - Malignancy |
| - Ischemia | - Neurogenic bladder |
| - Atherosclerosis | - C-section or other uterine surgery |
| - PID/infection | - Pessary use |
| - RADs | - Endometriosis |
| - Steroid use | - Endocervical conization |

DDx of clear vaginal fluid after TAH

→ “SLUTS Pee”

- Seroma
- Lymph
- Urine
- Tube fluid (Fallopian)
- Spontaneous vaginal secretions
- Peritoneal fluid

Different types of interposition flaps used in VVF repair

→ “MOP GIRLS”

- Martius
- Omental
- Peritoneal
- Gracilis muscle
- Intestinal seromuscular
- Rectus abdominis
- Labial myocutaneous
- Skin (gluteal)

RFs for ureterovaginal fistulae

→ “Fat SPERM”

- Fat (obese)
- Surgery (pelvic)
- PID
- Endometriosis
- RADs
- Malignancy (pelvic)

Syndromes associated with bladder diverticula

→ “FEW Men”

- Fetal alcohol syndrome
- Ehlers-Danlos
- Williams
- Menkes

Indications for surgical management of bladder diverticula

→ “Cut Out Very Slowly SIR”

- Cancer
- Obstruction of upper tracts
- VUR
- Stones
- Symptoms persist
- Infections persist
- Renal deterioration

Different types of urethral diverticula

→ “Simple Saddles at the Circus”

- Simple
- Saddle
- Circumferential

Diseases found in urethral diverticula

→ “MENS”

- Malignancy
- Endometriosis
- Nephrogenic adenoma
- Stones

INFECTIONS

Factors that suggest a “complicated” UTI

→ “ACADEMIC WHIP”

- Abx use (recent or current)
- Catheterized patient
- Abnormal GU tract (eg neurogenic bladder, diverticulum, etc)
- DM
- Elderly
- Male
- Immunosuppression
- Child
- Week long symptoms at presentation
- Hospital acquired UTI
- Instrumentation (recent)
- Pregnancy

Bacterial virulence factors that increase likelihood of UTIs

→ “Hokus POKE-US”

- Hemolysin & Hemagglutination
- P pili or P fimbriae
- O antigen
- K antigen
- Exotoxin production
- Urease production
- Siderophore production

Host (urinary) factors that decrease likelihood of UTIs

→ “LOCAL Grown STUUF”

- | | |
|------------------------|---|
| - Lactobacillus | - Salts (high) |
| - Organic acids (high) | - Tamm-Horsfall proteins |
| - Cytokines & PMNs | - Urea (high) |
| - Acidic urine pH | - Umbrella cell shedding |
| - Lactoferrin | - Flow of dilute urine (most important) |
| - Glucose (low) | |

Correctable causes of bacterial persistence.

→ “PUFFED UP MASK”

- | | |
|---------------------------|---|
| - Papillary necrosis | - Urachal cyst (infected) |
| - Ureteral stump | - Prostatitis (chronic) |
| - FB | - MSK |
| - Fistulae | - Abscess (perivesical, perinephric) |
| - Ectopic ureter | - Stones (infected) → most common cause |
| - Diverticulum (urethral) | - Kidney (atrophic segment) |

Conditions associated with renal papillary necrosis

→ “POST CCAARRDD”

- | | |
|----------------------------|------------------------------|
| - Pyelonephritis (chronic) | - Cirrhosis |
| - Obstruction (chronic) | - Candidal infection (renal) |
| - Sickle cell disease | - Analgesic abuse |
| - TB | - Amyloidosis |
| | - Renal Tx rejection |
| | - Renal vein thrombosis |
| | - DM |
| | - Dehydration |

GU Manifestations of sickle cell disease

→ “HUGE F⁺N PRIAPISM”

- Hematuria
- UTIs
- Glomerular disease
- ED
- Frequency, polyuria, etc (nephrogenic DI)
- Nocturnal enuresis
- Priapism
- RTA (distal)
- Infertility
- ARF
- Papillary necrosis
- Infarcts (renal medulla, testicular)
- Slow (chronic) renal failure
- Medullary RCC

Indications to image patient with acute pyelonephritis

→ “Pyelo Probably SOUNDS Refractory”

- Papillary necrosis
- PCKD and ESRD
- Stone history (especially struvite)
- Obstruction possible
- Unusual infecting organism
- Neurogenic bladder
- DM
- Surgery that predisposes to obstruction (diversion, URS, etc)
- Refractory to appropriate ABx

Antibiotics that are bactericidal

→ “Stronger, Better Mother F⁺N Abx”

- Septra
- Beta-lactams (penicillins, cephalosporins, carbapenems)
- Metronidazole
- Fluoroquinolones
- Nitrofurantoin
- Aminoglycosides

Antibiotics contraindicated in renal failure

→ “Never Ever Take Sulfa Meds”

- Nitrofurantoin
- Ethambutol
- Tetracycline
- Sulfa (long-acting)
- Methenamine

Antibiotics that do not need renal dosing

→ “KAMI Avoids Renal Dosing on C4”

- | | | |
|----------------|------------------|-------------------|
| - Ketoconazole | - Amphotericin B | - Ceftriaxone |
| - Azithromycin | - Rifampin | - Clindamycin |
| - Moxifloxacin | - Doxycycline | - Cloxacillin |
| - INH | | - Chloramphenicol |

*** Flagyl & Erythromycin if CrCL <10

GU Manifestations of DM

→ “Bladder VENUE”

- Bladder cystopathy
- Vascular renal disease
- ED
- Nephropathy
- UTIs
- Emphysematous pyelonephritis/cystitis

Side effects of amphotericin B

→ “AAAMMMPPPHHO B”

- | | |
|--|-------------------------------|
| - Anemia | - HypoK |
| - Anaphylaxis | - HypoCa |
| - Arrhythmias | - HypoMg |
| - Myalgia/flu-like symptoms | - Ototoxicity |
| - Multi-organ failure (hepatotoxicity) | - Bean toxicity (nephrotoxic) |
| - Microcephaly (only congenital anomaly) | |
| - Phlebitis | |
| - Pain | |
| - Platelets ↓'d (thrombocytopenia) | |

RFs for Fournier's gangrene

→ “DAMPPP SCROOTI”

- | | |
|---------------------|--------------------------------|
| - DM | - Surgery in local area |
| - Alcohol abuse | - CIC (urethral extravasation) |
| - Malnutrition | - Roids |
| - PVD | - Obese |
| - Paraphimosis | - Old age |
| - Peri-anal disease | - Trauma |
| | - Immunosuppression (eg HIV) |

Potential causes of prostatitis

→ “MIMIC Dick PAIN”

- Multi-factorial cause
- Intraductal reflux
- Microbiologic cause
- Immunologic alteration
- Chemical-induced inflammation
- Dysfunctional voiding
- Psychologic cause
- Altered prostatic host defenses (“CAT PUBES”)
- Interstitial cystitis-like cause
- Neural dysregulation

Causes of altered host defenses that can lead to prostatitis

→ “CAT PUBES”

- Catheter
- Anal sex (unprotected)
- TURP/TRUS Bx
- Phimosis
- UTIs
- Blood groups
- Epididymitis (acute)
- Secretory dysfunction

Minimal investigations for prostatitis

→ “HUU, SQUU” (mandatory, recommended)

- History & Physical
- Urinalysis
- Urine culture
- Stamey 4-glass test
- Questionnaire (CPSI)
- Uroflow & PVF
- Urine cytology

Medical treatment options for prostatitis

→ “AAA Meds Help Alleviate Prostatitis Problems” } RCT benefit only for α -blockers, anti-inflammatories & phytotherapy

- Abx
- Alpha-Blockers
- Anti-inflammatories (NSAIDs, steroids, etc)
- Muscle relaxants (eg baclofen)
- Hormonals (eg finasteride, estrogen, etc)
- Allopurinol
- Phytotherapy (eg Saw Palmetto, Quercetin, etc)
- Pentosan polysulfate (Elmiron)

Non-medical treatment options for prostatitis

→ “SAME Bullshit Procedures for Prostatitis Problems”

- Surgery (TUNA, TUMT, TUIBN, TURP, etc)
- Acupuncture
- Massage of prostate
- Ejaculate frequently
- Biofeedback
- Psych support
- PFMT/trigger point release
- Pudendal nerve entrapment therapy

Conditions associated with IC/PBS

→ “ASS IF Vestibulitis”

- Allergies
- Sjogren's
- SLE
- IBD/IBS
- Vulvar vestibulitis

Potential causes of IC/PBS

→ “My Infected ANUS Leaks”

- Mast cell activation
- Infectious cause (chronic)
- Autoimmune cause
- Neurogenic inflammation
- Urine toxicity (increased APF in urine)
- Stress or psychological cause
- Leaky epithelium or GAG

DDx of a +ve intravesical KCl test

→ “I CROUP”

- IC
- CPPS
- Radiation cystitis
- OAB
- UTI
- Prostatitis (chronic)

DDx of bladder glomerulations

→ “DIRECT”

- Diversion
- IC/PBS
- Radiation cystitis
- ESRD with low urine output (dialysis)
- CIS
- Toxic chemotherapy/chemicals

Different questionnaires to assess IC/PBS

→ “WOP”

- Wisconsin Univ. IC scale
- O’Leary-Sant IC scale
- PUF symptom scale

Conservative treatments for IC/PBS

→ “AWE, Poor Bladder’s MAD”

- Abx (empiric course)
- Watchful waiting
- Education & empowerment
- PFMT + biofeedback
- Behaviour therapy (bladder retraining, voiding diary, stress reduction, exercise, etc)
- Massage (soft tissue)
- Acupuncture
- Dietary changes

Potential oral therapies for IC/PBS

→ “PATCH It N’ GO” } RCT proven for “PACH”

- Pentosan polysulfate (Elmiron)
- Amitriptyline
- Topiramate
- Cimetidine
- Hydroxyzine (Atarax)
- Immunosuppression (steroids, cyclosporine, etc)
- NSAIDs
- Gabapentin
- Opioids

Potential intravesical therapies for IC/PBS

→ “Little SHePherD B” } RCT proven for “PD”

- Lidocaine
- Silver nitrate
- Heparin
- Pentosan polysulfate
- DMSO
- Botox injections

Last resort therapies for refractory IC/PBS

→ “THE NARC”

- TENS
- Hydrodistension
- Epidural blocks (lumbar)
- Neurostim device
- Acupuncture
- Resection of Hunner’s ulcers
- Cystectomy

Sexually transmitted causes of genital ulcers

→ “Suck The Penis (Dry), Chew Her Anus (Clean), Hump Her Ass (Fast), Lick Cheese Dick (Enjoy)”

- Syphilis = Treponema pallidum = Pen G (Doxy)
- Chancroid = Hemophilus ducreyi = Azithro (Cipro/Ceftriaxone)
- Herpes = HSV type 2 = Acyclovir (Famciclovir)
- Lymphogranuloma venereum = Chlamydia trachomatis = Doxy (Erythromycin)

	S	C	H	L
lesion	single	bilateral	bilateral	single
symptoms	painless	painful	painful	painless
nodal symptoms	painless	painful	painful	painful
nodes	bilateral	unilateral	bilateral	unilateral

Non-sexually transmitted causes of genital ulcers

→ “Big FAT CLERC”

- Behcet’s syndrome
- Fixed drug reaction
- Amebiasis
- Trauma
- Cancer
- Lichen planus
- Erythema multiforme
- Reiter’s
- Crohn’s

Non-malignant GU manifestations of HIV

→ “SUPER SOFT HIVAN”

- STDs (syphilis, Chancroid, herpes, etc)
- Urethritis (gonorrhea, Chlamydia, etc)
- Prostatitis
- Epididymitis (CMV, toxoplasmosis, etc)
- Renal infections (TB, CMV, etc)
- Stones (indinivir)
- Orchitis (CMV, toxoplasmosis, etc)
- Fournier’s gangrene
- Testicular atrophy
- Hematuria
- Impetigo
- Voiding dysfunction (AUR, OAB, BOO, etc)
- Abscesses
- Nephropathy (HIVAN)

Malignancies associated with HIV

→ “Catch Kaposi’s PALS Live on MTV

- Cervical
- Kaposi’s sarcoma
- Penile Ca
- Anal Ca
- Lymphoma (NHL, Hodgkins, primary CNS, etc)
- Skin Ca (non-melanomatous)
- Lung Ca
- Myeloma
- Testicular Ca
- Vulvar Ca

RFs for reactivation of dormant TB

→ “SID Activates Dormant TB”

- Steroids
- Immunosuppression
- DM
- AIDS
- Debilitating disease
- Trauma

RFs for Candida albicans UTI

→ “CANDIDA SMC”

- Catheterized
- Abx use
- Neurogenic bladder
- DM
- Impaired urine flow
- Diversions (eg ileal conduit)
- Anomalous GU tract
- Steroids
- Malnutrition
- Cancer

Medications that interact with oral antifungals (-azoles)

→ ↓'s [-azole] } “ASH falls down”

→ ↑'s [-azole] } “RIP it up”

→ ↑'s [co-administered drug] } “Pills Will Surge Serum Concentration Dude”

- Antacids
- Sucralfate
- H₂ blockers

- Rifampin
- INH
- Phenytoin

- Phenytoin
- Warfarin
- Sulfonylurea drugs
- Statins
- Cyclosporine
- Digoxin

INFERTILITY

Components of blood-testis barrier

→ “Semen Can't Pass”

- Sertoli cell tight junctions
- Capillary endothelial cells
- Peritubular myoid cells

Components of seminal fluid

→ “Fresh SPICEZ”

- Fructose
- Semen, Spermin,
- PGs, PSA, proteins (seminogelin), phosphates
- Immunoglobulins
- Citric acid
- Esterases
- Zinc

Lung diseases associated with male infertility

→ “SYCK”

- Sarcoidosis
- Young's syndrome
- CF
- Kartagener's syndrome

DDx of low volume semen analysis

→ “Inadequate FOR Life”

- Inadequate collection
- Failure of emission (SCI, DM, RPLND, psych, etc)
- Obstruction (CBAVD, ED cyst, etc)
- Retrograde Ejaculation (DM, α -blockers, TUIBN, etc)
- Low production (hypogonadism)

DDx of azoospermia

→ Pre-testicular cause } “ICE Pick Pituitary”

- Idiopathic
- Congenital (Kallman’s, Prader-Willi, Laurence-Moon-Biedl-Bardet, CHARGE, etc)
- Estrogen excess (Leydig cell tumour, Sertoli cell tumour, obesity, adrenal tumour, etc)
- Prolactin excess (pituitary tumour, hyperT4, estrogens, etc)
- Pituitary (tumour, surgery, radiation, trauma, infection, etc)

→ Testicular cause } DUNKY XX (congenital) ... TV OGR (acquired)

- | | |
|------------------------------|---|
| - Downs | - Torsion |
| - UDT | - Varicocele |
| - Noonan’s | - Orchitis (viral) |
| - Klinefelter’s | - Gonadotoxins (chemo, macrobid, sulfasalazine, CCBs, cocaine, etc) |
| - Y microdeletions | - RADs |
| - XX maleness, XYY supermale | |

DDx of asthenospermia

→ “VAG PPISSS”

- | | |
|----------------------------|---|
| - Varicocele (most common) | - Prolonged abstinence |
| - Anti-sperm Ab’s | - Partial obstruction (eg EDO) |
| - GU infection | - Idiopathic |
| | - Sperm ultrastructural defects (eg Kartagener’s) |
| | - Systemic illness |
| | - Spermicide use |

DDx of oligoasthenospermia (OAT)

→ “VIP USED OAT”

- Varicocele
- Idiopathic
- Partial obstruction (eg EDO)
- UDT
- Systemic illness
- Endocrine abnormalities
- Drugs, heat, toxins, etc

RFs for developing Anti-sperm Ab’s

→ Very Careful BUT GOT Antibodies

- Varicocele
- Cancer
- Biopsy or surgery
- UDT
- Torsion
- GU tract infection
- Obstruction of ductal system
- Trauma
- Anal intercourse (receptive)

RFs for abnormal sperm DNA

→ “Infertility FACTS”

- Infertility (male)
- Fever
- Air pollution
- Cancer
- Toxic industrial exposure
- Smoking

Drugs or medications associated with abnormal spermatogenesis

→ “Cocaine & Marijuana SNACKS”

- Cocaine
- Marijuana
- Smoking
- Sulfasalazine
- Nitrofurantoin
- Anti-androgens
- Alcohol
- Cimetidine
- Colchicine
- CCBs
- Chemotherapeutics
- Ketoconazole
- Steroids
- Spironolactone

ANDROLOGY

7 stages of erection and detumescence

→ “LT FRIS Fast”

- Latent phase
- Tumescence
- Full erection
- Rigid erection
- Initial detumescence
- Slow detumescence
- Fast detumescence

Medications that can cause ED

→ “7A’s CHOP Dick”

- | | | |
|----------------------|-------------------------------------|---------------------------|
| - Anti-HTN’sives } | diuretics & β -blockers worst | - Chemo |
| - Alpha-agonists } | methyldopa, clonidine | - H ₂ blockers |
| - Anti-androgens } | 5ARIs, flutamide, etc | - Opioids |
| - Anti-psychotics } | resperidone, clozapine | - Protease inhibitors |
| - Anti-depressants } | TCA’s, SSRIs, MAOIs | - Digoxin |
| - Anxiolytics } | benzo’s | |
| - Alcohol abuse | | |

Causes of ED in patients with renal failure (ESRD)

→ “PAPA Has ED”

- Psychologic
- Atherosclerosis accelerated
- Prolactin elevated
- Autonomic neuropathy
- HP axis disturbances
- Endothelial Dysfunction causing ↓’d NO bioavailability

Indications for specialized testing for ED

→ “PETER Penis Loves SPORT”

- | | |
|-----------------------------------|-------------------------------|
| - Peyronie’s | - Pre-op |
| - Early onset (primary ED) | - Legally sensitive case |
| - Trauma to pelvis or perineum | - Sleep disorder suspected |
| - Endocrine abnormality (complex) | - Psychogenic cause suspected |
| - Relationship problems | - Obscure cause of ED |
| | - Refractory to therapy |
| | - Trial setting |

Indications for nocturnal penile tumescence (NPT) testing in ED

→ “Penis Loves SPORT”

- Pre-op
- Legally sensitive case
- Sleep disorder suspected
- Psychogenic cause suspected
- Obscure cause of ED
- Refractory to therapy
- Trial setting

Potential side effects of androgen replacement therapy

→ “ABC PPIGS”

- Acne
- Balding (male pattern)
- Cholesterol changes
- Polycythemia
- Priapism
- Platelet aggregation ↑’s
- Infertility (LH & FSH suppression)
- Gynecomastia
- Sleep apnea

Absolute contraindications to androgen replacement therapy

→ “CHEAP Breastest Sluts”

- CHF (class 3 or 4)
- Hct >55%
- Elevated PSA not investigated
- AbN DRE not investigated
- Prostate Ca
- Breast Ca
- Sleep apnea
- LUTs (severe – IPSS >19)

Medications used to treat premature ejaculation

→ “Slower Cum with Premature Ejaculation Therapy”

- SSRIs } Paxil (1st line), Sertraline, Fluoxetine
- Clomipramine (TCA)
- PDE5 inhibitors (if concurrent ED)
- EMLA cream
- Tramadone (SNRI)

Contraindications to insertion of a penile prosthesis for ED

→ “Can’t Insert Dick Prosthesis”

- Coagulopathy (uncontrolled)
- Infection (active)
- DM (uncontrolled)
- Poor surgical candidate

Complications of penile prosthesis insertion

→ “Old MAIMED Penis”

- Over-sized cylinder/rod
- Mechanical failure
- Auto-inflation
- Infection
- Migration of pump
- Erosion
- Deformity (SST)
- Perforation

Diseases associated with Peyronie's disease

→ "Damn Painful Twisted Penis"

- Dupuytren's contractures
 - Plantar fasciitis
 - Tympanosclerosis
 - Paget's
- (?? DM, gout, trauma, etc)

Oral Medications used to treat Peyronie's disease

→ "Little Effective Treatment for Curve Penis"

- L-carnitine
- Vitamin E
- Tamoxifen
- Colchicine
- Potaba

Intralesional medications used to treat Peyronie's disease

→ "CIC"

- CCBs
- IFN
- Collagenase

Causes of priapism

→ "TIN TIN Meds"

- Thromboembolic causes ("SLATE") } Sickle cell, Leukemia, Asplenia, TPN, Epo
- Iatrogenic (ICI)
- Neoplastic
- Trauma
- Infections (malaria, rabies, scorpion bites)
- Neurogenic
- Meds

Medications that can cause priapism

→ "7As 2Ts"

- Anti-HTNs } hydralazine, α -blockers
- Anti-coagulants } heparin, coumadin
- Anti-histamines } hydroxyzine
- Anti-psychotics } clozapine
- Anti-depressants } trazadone
- Androgens
- Alcohol
- Tranquilizers
- Tacrolimus

Medications used to treat stuttering priapism

→ "Viagra TAMED HIS Boner"

- Viagra
- Terbutaline
- Anti-androgens } 5ARIs, casodex, etc
- Methylene Blue (high-flow)
- Estrogen
- Digoxin
- Hydroxyurea (sickle cell)
- ICI (self-injections)
- Streptokinase
- Baclofen

NEPHROLOGY

Main functions of the kidney

→ “WEB DECAF”

- Waste excretion
- Electrolyte balance
- BP control
- Drug metabolism
- Epo production
- Calcium balance (Vit D)
- Acid base balance
- Fluid homeostasis

Hormonal substances that cause vasoconstriction of the renal vasculature

→ “A VANE”

- AT II
- Vasopressin
- ANP
- NE
- Endothelin (most potent)

Hormonal substances that cause vasoDILATION of the renal vasculature

→ “NO CO GAPS”

- NO
- CO
- Glucocorticoids
- Acetylcholine
- PGE₂
- Serotonin

Causes of nephrogenic DI

→ “OLD CAARP FISH”

- | | | |
|-------------------------|----------------------------|------------------------|
| - Obstruction (chronic) | - Calcium excess (hyperCa) | - Familial X-linked DI |
| - Lithium | - Ampho B | - Idiopathic |
| - Demeocycline | - Amyloidosis | - Sick cell |
| | - Renal failure | - HypoK |
| | - PCKD | |

Causes of acquired distal RTA

→ “POST CLAAASHH”

- | | |
|----------------------------|--|
| - Pyelonephritis (chronic) | - Cirrhosis |
| - Obstruction (chronic) | - Lithium |
| - Sick cell | - Analgesic abuse |
| - Transplant Rejection | - ATN |
| | - Autoimmune disease (thyroiditis, Sjogren's, SLE) |
| | - Sarcoidosis |
| | - HyperPTH'ism |
| | - Hypercalciuria (familial) |

Causes of Allergic Interstitial Nephritis (AIN)

→ “3C PORN ATLAS”

- | | |
|------------------|---------------|
| - Cephalosporins | - Allopurinol |
| - Cipro | - Thiazides |
| - Cimetidine | - Lasix |
| - Penicillins | - ASA |
| - Omeprazole | - Sulfa drugs |
| - Rifampin | |
| - NSAIDs | |

Indications for dialysis

→ “OK PUMP”

- Overload
- hyperK
- Pericarditis (uremic)
- Uremic symptoms (encephalopathy, seizures, neuropathy, etc)
- Metabolic acidosis
- Poisons

Indications to start RRT acutely in hospitalized patients

→ “AA OK ON PUMP”

- Azotemia (BUN >30)
- Anuric
- Overload
- hyperK
- Oliguria (<200cc/12h)
- Na abnormalities (Na >160 or <115)
- Pericarditis (uremic)
- Uremic symptoms (encephalopathy, seizures, neuropathy, etc)
- Metabolic acidosis
- Poisons

Features associated with AD PCKD

→ “Be DA Real MVP with 8 aCYSTs”

- Berry aneurysms
- Diverticulitis
- Aortic arch aneurysms
- Renal artery aneurysms
- MV prolapse
- cysts } kidney, liver, spleen, pancreas, lung, arachnoid, pineal gland, SVs

Causes of ESRD that recur after renal Tx

→ “FOH, FAC, DI, PAD”

- FSGS
 - Oxalosis
 - HUS
 - Fabry's
 - Amyloidosis
 - Cystinosis
 - DM
 - IgA
 - PCKD
 - Alport's without anti-glomerular BM Ab's
 - Dysplasia
- } recurs and can lead to graft failure
- } recurs but can be manageable
- } recurs but does not cause graft failure

Causes of HTN

→ “Essential AORTTA”

- Essential HTN
- Aortic coarctation
- OCP
- Renal causes } parenchymal disease, renovascular disease
- Toxemia of pregnancy
- T4 excess
- Adrenal causes } Cushing's, Conn's, Pheo

Endogenous stimulators of renin release

→ “Salty BP BP”

- ↓ NaCl in macula densa
- ↓ Blood volume (JG stretch)
- ↓ Perfusion pressure
- ↑ β -adrenergic activity
- ↑ PGs

Features suggestive of true renovascular HTN

→ “A FARMERSS BP”

- Age (<30 or >55 yrs at onset)
- Family History – ve
- Atherosclerosis elsewhere (CAD, CVD, carotid disease, etc)
- Renal insufficiency with ACE inhibitor
- Medication refractory
- Extreme HTN (malignant HTN, accelerated HTN, etc)
- Retinopathy from HTN
- Smoker
- Sudden onset, short duration
- Bruit (abdominal)
- Pulmonary edema

RFs predictive of atherosclerotic RAS

→ “A CCCP FAD”

- Age >55yrs at onset
- CAD
- CHF
- Creatinine elevated
- PVD
- Female
- Azotemia progressive after control of BP with meds
- DM

Signs of renal salvageability in patient with complete RAS occlusion causing IN

→ “Can Save GFR”

- Creatinine <350 g/L (US <4mg/dL)
- Size >9cm
- Glomeruli well preserved on Bx
- Function seen on nuclear scan or IVP
- Retrograde filling by collaterals seen on angiography

Causes of renal artery aneurysms

→ “PICK ME MAMA”

- | | | |
|------------------------------|-----------------|------------------------------|
| - Polyarteritis nodosa | | - Medial FD (microaneurysms) |
| - Iatrogenic (Bx, PCNL, PNx) | - Marfan's | - Atherosclerotic |
| - Congenital | - Ehlers-Danlos | - Mycotic (infections) |
| - Kawasaki's disease | | - AD PCKD |

Indications for surgical management of a renal artery aneurysm

→ “WEBBERRRS DIC”

- Woman of childbearing age with potential for pregnancy
- Embolization from thrombus
- Bigger than 2cm
- BP uncontrolled
- Enlarging on imaging
- Renal ischemia
- Ruptured
- functionally significant RAS
- Symptomatic (flank pain, hematuria, etc)
- Dissecting aneurysms
- Incomplete calcification

Indications for surgical management of a renal AVF

→ “CHHERR”

- CHF (severe)
- HTN (uncontrolled)
- Hematuria (recurrent)
- Enlarging on imaging
- Renal deterioration
- Rupture (retroperitoneal bleed)

Causes of renal artery thrombosis

→ “FAT Pig SAT UP”

- FD of renal artery
- Atherosclerosis of aorta or renal artery
- Trauma
- Polycythemia
- Syphilis
- Angiography (aorta or renal)
- Thromboangiitis obliterans
- Umbilical artery catheterization in neonate
- Polyarteritis

Causes of renal artery embolism

→ “MAP TO embolism AVE”

- MI
- A-fib
- Paradoxical embolism (VSD, ASD)
- Tumour (cardiac)
- Open heart surgery
- Aneurysms } saccular renal artery or ventricular
- Valve vegetations
- Endocarditis (bacterial)

Causes of branch renovascular disease

→ “A FAT TAN”

- Aneurysm
- Fibrous dysplasia (FD)
- AVM
- Trauma
- Takayasu's arteritis
- Atherosclerosis (very rare)
- Neurofibromatosis

Contraindications to renal Tx

→ “I PUNT BAC”

- Infections (active)
- Poor surgical candidate (high chance of M&M)
- Urologic or vascular conditions that make Tx technically not feasible
- Neoplasm (active or recent)
- T cell crossmatch +ve
- Brain injury (irreversible)
- ABO incompatible
- Compliance issues or substance abuse

Indications for pre-Tx nephrectomy

→ “MASHHH PPPP”

- Malignant mass
- Anti-glomerular BM Ab's (persistent)
- Stones not amenable to minimally invasive treatment
- HTN (refractory)
- Hematuria (refractory)
- Hydronephrosis (high grade)
- PCKD with limited space for transplant
- Proteinuria (refractory)
- Pyelonephritis (recurrent)
- Polyuria (refractory)

Contraindications to donating your kidney for Tx

→ “Robinette WON'T Make Cut” } ABO incompatibility, +ve crossmatch, anatomic abnormalities are all RELATIVE now

- Renal disease (active or risk of future disease)
- Work-up reveals abnormality
- Operative risk too high
- Neoplasm
- Transmissible infection
- Mental dysfunction
- Coerced or financial gain involved

Complications related to renal Tx & immunosuppression

→ “GIVE U Real Complications”

- GI
- Infectious
- Vascular
- Endocrine
- Urinary
- Rejection
- Cancers

Most common secondary malignancies associated with renal Tx & immunosuppression

→ “SLK Really Vain Car”

- Skin Ca
- Lymphoma (NHL most common)
- Kaposi's
- RCC
- Vulvar Ca
- Cervical Ca

Non-surgical causes of post-renal Tx lymphocele

→ “Real BAD PASS”

- Rejection
- Bx
- AV fistula
- Diuretics
- PCKD
- Anticoagulant use (high doses)
- Steroids (high doses)
- Sirolimus use

Causes of ED after renal Tx

→ “SCANT Erections”

- Smooth muscle (cavernosal) dysfunction
- Central effects (eg anxiety)
- Arterial blood supply diminished (atherosclerosis)
- Neurogenic causes (autonomic problems – DM)
- Tunica albuginea dysfunction (Peyronie’s from propranolol)
- Endocrine problems (low T)

Transplant-related medications that cause ED

→ “Transplant Pills Cause Soft Cock”

- Tacrolimus (smooth muscle)
- Prednisone (endocrine, arterial)
- Cyclosporine A (endocrine, arterial, smooth muscle)
- Sirolimus (endocrine)
- Cimetidine (endocrine)

Management options for ED in patients with renal Tx

→ “Let’s Make A VIP Virile”

- Lifestyle modifications & counseling } stop smoking, stop EtOH, etc
- Medication changes } if possible, avoid β -blockers, cimetidine, glucocorticoids
- Add medications } testosterone, PDE5 inhibitors, T4 replacement
- Vacuum device
- ICI
- Penile prosthesis
- Vascular procedures } revascularization, angioplasty

Pre-requisites prior to insertion of a penile prosthesis for renal Tx patient with ED

→ “My RIGID PP”

- Minimize tissue dissection
- Rejection free for ≥ 6 mos
- Infection free (skin or urine)
- Graft function stable
- Immunosuppressants at lowest possible doses
- Device with low probability of malfunction
- Prophylactic Abx for 2wks post-op
- Perivesical reservoir contraindicated

ONCOLOGY

RFs for bladder TCC

→ “COBRA SCARS”

- Cyclophosphamide
- Occupational exposure
- Blackfoot disease
- RADs
- Aristolochia fangchi
- Smoking
- Chronic UTIs
- Analgesic abuse
- Renal Tx
- Schisto

RFs for bladder SCC

→ “Some Say Schisto Can Can Bladder Disease”

- Smoking
- Stones
- Schisto
- Chronic catheter
- Chronic UTIs
- BCG
- Diverticulum (bladder)

RFs for bladder adenocarcinoma

→ “UCC CUBE”

- Urachal cyst/remnant
- Chronic UTIs
- Cystitis glandularis
- CIS
- Ureterosigmoidostomy
- Bladder augment
- Exstrophy

RFs for upper tract TCC

→ “COBRA SCALP”

- Cyclophosphamide
- Occupational exposure
- Balkan nephropathy
- RADs
- Aristolochia fangchi
- Smoking
- Chronic UTIs
- Analgesic abuse
- Lynch syndrome 2
- Papillary necrosis

Non-epithelial tumours of the bladder

→ “SNL MY Pheo”

- Sarcoma (leiomyosarcoma most common, RMS)
- Neurofibroma
- Lymphoma
- Melanoma
- Yolk sac tumour
- Pheochromocytoma

Contraindications to intravesical BCG therapy

→ ABSOLUTE } “A BIG TIT”

→ RELATIVE } “TULIPP”

- Autoimmune disease (active)
- BCG sepsis previously
- Immediately after TURBT
- Gross hematuria
- Total incontinence
- Immunocompromised
- Traumatic catheterization
- TB
- UTI
- Liver disease
- Increased age
- Pregnancy
- Poor performance status

Indications for early/timely radical cystectomy for superficial bladder cancer

→ Let's DUMP T1G3, ABC"

- LVI
- Diverticulum with high grade TCC
- Ureteral or Urethral involvement
- Multifocal CIS
- Patient preference
- T1G3 disease
- Access issues (urethral disease, too much tumour, bladder too capacious, etc)
- BCG-refractory
- Crippled bladder

Indications for Radical Cystectomy for bladder Ca in a male

→ "PIPE"

- Prostatic stromal TCC
- Invasive disease (localized)
- Palliative for metastatic bladder Ca
- Early cystectomy ("Let's DUMP T1G3, ABC)

Indications for Radical Cystectomy for bladder Ca in a female

→ "PIE"

- Palliative for metastatic bladder Ca
- Invasive disease (localized)
- Early cystectomy ("Let's DUMP T1G3, ABC)

Contraindications to Ileal conduit

→ "SIR"

- Short bowel syndrome
- IBD of small bowel
- RADs to ileum

Contraindications to Colon conduit

→ "RIDD"

- RADs to colonic segment
- IBD of colon
- Diarrhea (severe chronic)
- Diverticulitis for (sigmoid conduit)

Contraindications to an orthotopic neobladder

→ "RUM (absolute) RAIDS the Liver (relative)"

- | | |
|-------------------------------------|---------------------------------------|
| - Renal failure | - RADs |
| - Urethral TCC | - Age or life expectancy |
| - Margins +ve at time of cystectomy | - IBD |
| | - Dexterity issues (unable to do CIC) |
| | - Short gut syndrome |
| | - Liver failure |

Contraindications to a continent cutaneous reservoir

→ "Rum RAIDS the Liver

- Renal failure
- RADs to segment
- Age or life expectancy
- IBD
- Dexterity issues
- Short bowel
- Liver failure

Contraindications to a continent rectal reservoir

→ “RURAL Diverticulitis”

- Renal failure
- Ureteric dilatation
- RADs (pelvic)
- Anal sphincter incontinence
- Liver disease
- Diverticular disease

Types of non-refluxing uretero-colonic anastomoses

→ “GSP Leadbetter”

- Goodwin
- Strickler
- Pagano
- Leadbetter-Clark

Types of uretero-enteric anastomoses

→ BW (refluxing) SLUT Hammock (non-refluxing)”

- Bricker
- Wallace
- Split nipple
- Le Duc
- Ureteral compression Ghoneim
- Tunneled
- Hammock

Indications for a partial cystectomy

→ “Don’t Do Partial Unless All Biopsies Safe”

- Diverticulum +/- tumour
- Dome TCC (solitary)
- Pheo (primary bladder)
- Urachal adenocarcinoma
- Adjacent tumour invasion
- Benign bladder disease (Hunner’s ulcer, leiomyoma, etc)
- Sarcoma (primary)

Contraindications to partial cystectomy

→ “Can’t Mend (absolute) Bladder HULC (relative)”

- | | |
|-----------------------------|--|
| - CIS elsewhere in bladder | - High grade |
| - Multifocal tumour | - Ureteral reimplant required |
| - BN or trigone involvement | - Lymphadenopathy |
| | - Capacity issues (poorly functioning bladder) |

Indications for a simple cystectomy

→ “RIP & INFECT”

- Radiation cystitis (refractory)
- Incontinence (severe and refractory)
- Pyocystis
- IC (refractory to all other Rx)
- Neurogenic bladder (refractory)
- Fistula (large and refractory)
- Exenteration (as part of treatment for another pelvic malignancy)
- Cyclophosphamide cystitis (refractory)
- Trauma to urethra (severe and refractory)

Metabolic complications of urinary intestinal diversions

→ “G-DIVERSIONS”

- Growth retardation
- Drug metabolism problems
- Infections
- Vit B12 deficiency
- Electrolyte abnormalities
- Renal failure
- Stones
- Intestinal problems
- Osteomalacia
- Neoplasms
- Sensory alterations (neuropathy)

Findings suggestive of an IVC thrombus

→ “MAP out a PLAN for Vein”

- Murmur in R atrium (mass)
- Abdo veins (superficial) dilated
- PE
- Proteinuria
- Lower limb edema
- Ascites
- Non-functioning kidney
- Varicocele on R side, or one that doesn't collapse with recumbency

Most common tumours that metastasize to the kidney

→ “Liver Bx G'day Mate”

- Lung
- Breast
- GI tract
- Melanoma

Indications for a simple nephrectomy

→ “STOP Don't Take Radical Approach Please”

- Stones
 - Trauma
 - Obstruction
 - Pyelo (chronic)
 - Donor Nx
 - Tx rejection
 - RVH
 - Adjacent tumour (Sarcoma, testicular LNs, etc)
 - PCKD
- \ / contralateral N kidney with unilateral irreversibly damaged kidney

Premalignant cutaneous penile lesions

→ “Beware, Pinkus Causes Penile Cancer Later”

- BXO
- fibroepithelial polyp of Pinkus
- Cutaneous horn
- Pseudoepitheliomatous Micaceous & Keratotic balanitis
- Condyloma acuminatum
- Leukoplaki

RFs for penile cancer (SCC)

→ “Penile Cancer Has BURST”

- Phimosis
- CIS
- Hygiene problems
- Beware, Causes Penile Cancer Later (BXO, Condyloma, etc)
- Uncircumcised
- RADs
- Smoker, chewing tobacco
- Trauma

RFs for male urethral Ca

→ “Stupid BUSH”

- STDs
- Bladder Ca
- Urethritis
- Strictures of urethral
- HPV 16

RFs for female urethral Ca

→ “Diverticulum Probably Has Cancerous BLIP”

- Diverticulum
- Polyp
- HPV infections
- Caruncles
- Bladder Ca
- Leukoplakia
- Infections (chronic)
- Parturition

DDx of testicular microlithiasis

→ “ROC FIGSS”

- | | |
|------------|---------------|
| - RADs | - Fibrosis |
| - Orchitis | - Infarction |
| - Cancer | - Granuloma |
| | - Scar |
| | - Sarcoidosis |

Diseases associated with testicular microlithiasis

→ “DICK And NUT In V”

- | | |
|---------------------|---------------------|
| - Dysgenetic testes | - Neurofibromatosis |
| - Infertility | - UDT |
| - Cancer or CIS | - Torsion |
| - Klinefelters | - Infarcts |
| - AIDS | - Varicoceles |

RFs for testicular Ca

→ “His Cancer SURFACED”

- HIV
- Cancer in other testis
- Sexual ambiguity
- UDT
- Race (less in Blacks & Asians)
- Family Hx
- Age
- CIS
- Estrogen exposure in utero
- Dysgenetic testis

Testis tumours associated with elevated AFP & β HCG

→ “A-YET”

→ “B-SEC”

- | | |
|-------------------|-------------------|
| - Yolk Sac | - Seminoma |
| - Embryonal | - Embryonal |
| - Teratocarcinoma | - Choriocarcinoma |

RFs for prostate cancer

→ “SO FAR Prostate Disease Free”

- Smoking
- Obesity
- Family Hx
- Age
- Race
- Prostatitis, STDs
- Drinking EtOH
- Fatty diet

Different subtypes of prostate cancer

→ “Small Squirmy Men Don’t Like SLTS & Prostitutes”

- Small cell
- Squamous cell carcinoma
- Mucinous adenoCa
- Ductal adenoCa
- Lymphoma
- Sarcoma
- Leukemia
- TCC
- Signet ring
- Phylloides tumour

Subtypes of PCa that develop OSTEOLYTIC bone mets

→ “TSN”

- TCC
- Squamous
- Neuroendocrine (small cell)

DDx of small glands seen on TRUS Bx

→ “CABANAS Bx’d the SVs”

- Cancer
- ASAP
- Basal cell hyperplasia
- Atrophy
- Nephrogenic adenoma
- Atypical adenosis (benign)
- Sclerosing adenosis
- inadvertent Bx of SVs

Ectopic sources of PSA

→ “BALKS”

- Breast tissue (normal & malignant)
- Adrenal carcinomas
- Littre glands
- Kidney cancer
- Skene’s gland tumours

DDx of a HYPO-echoic lesion on TRUS

→ “The BLAAC SIGN”

- TCC
- Hematoma
- BPH nodule in TZ
- Lymphoma
- Abscess
- AdenoCa
- Cyst
- Sarcoid (post-RADs)
- Infarct
- Granuloma (post-TB)
- Normal tissue

DDx of a HYPER-echoic lesion on TRUS

→ “BAD SSS”

- Brachy seed
- Adipose tissue (periprostic)
- Ductal adenoCa
- Stones, calcifications
- SV involvement of tumour
- Squamous cell carcinoma

Complications of ADT for PCa

→ “ABCDEFGHIJKLMNOP”

- | | |
|-------------------------|-----------------------|
| - Anemia | - Increased lipids |
| - Bone loss & fractures | - J,K |
| - Cognitive decline | - Libido loss |
| - Depression | - Metabolic syndrome |
| - ED | - No muscle mass |
| - Fatigue | - Obesity |
| - Gynecomastia | - Personality changes |
| - Hot flashes | |

Medications used to treat hot flashes associated with ADT for PCa

→ “Each Capsule Gonna (non-hormonals) Cool Me Down (hormonals)”

- Effexor → 2nd line
- Clonidine
- Gabapentin
- Cyproterone acetate (steroidal anti-androgen)
- Megace (progesterone) → 1st line
- DES/Estradiol patch

Options for 2nd line hormone treatment in PCa

→ “SKATE Man”

- Steroids
- Ketoconazole
- Aminoglutethimide
- Tamoxifen
- Estrogen
- Megace

Options to treat osteoporosis related to ADT for PCa

→ “Let’s BCDE”

- Lifestyle modifications } wt loss, wt-bearing exercise, stop smoking, etc
- Bisphosphonates
- Calcium
- Vit D
- estrogen patch

CHEMO

Different classes of chemo

→ Antimetabolites } “GM-5”

- Gemcitabine
- MTX
- 5-FU

→ Plant Alkyls } “VET”

- Vincristine/vinblastine
- Etoposide
- Taxanes

→ Antibiotics } “-mycins”

- Adriamycin (doxorubicin)
- Bleomycin
- Mitomycin C
- Actinomycin C

→ Alkylating agent } “C’s IT”

- Cisplatin
- Carboplatin
- Cyclophosphamide
- Ifosfamide
- Thiotepa

Causes of hemorrhagic cystitis

→ “CRIS ... PACE BACKS CAR”

- Chemical } Penicillins, Allopurinol, Cyclophosphamide & Ifosfamide, Ether, NSAIDs, Bleomycin
- RADs
- Infectious } BK virus, Adenovirus, Candidal cystitis, KEEPS bacteria, Schisto
- Systemic diseases } Crohn’s, Amyloidosis, Rheumatoid arthritis

Management options for hemorrhagic cystitis

→ “Please BE A SAFE DOC”

- PGs
- Burn
- Elmiron
- Alum 1%
- Silver nitrate
- Amicar
- Formalin
- Embolization
- Diversion after cystectomy
- O2 hyperbaric
- Cold CBI

PEDIATRICS

Factors involved in testicular descent in the fetus

→ “GEGE-IG”

- Gubernaculum
- Endocrine factors } androgens, estrogens, MIS, descendin
- Genitofemoral nerve and calcitonin gene-related peptides
- Epididymis
- Intra-abdominal pressure
- Growth differential

Indications for in utero decompression of obstructive uropathy

→ “BUMKINNES”

- BOO suspected (bilateral hydronephrosis + oligohydramnios
- Urinary indices favorable } Na <110, Cl <100, Osmolality <210, β 2-microglobulin <10-20
- Male
- Karyotype normal
- Informed consent
- No evidence of other congenital anomalies
- No evidence of cystic kidneys
- Early onset oligo (20-25wks)
- Singleton

RFs for renal vein thrombosis in a child

→ “Premature SPUD CAN’T Dance”

- | | |
|------------------------------------|----------------------|
| - Prematurity | - Coagulopathy |
| - Sepsis | - Asphyxia |
| - Polycythemia | - Nephrotic syndrome |
| - Umbilical artery catheterization | - Trauma/tumour |
| - Dehydration | - DM mother |

Indications for prophylactic Abx for the GU tract in kids

→ “Before 2-3 mos, VIPs Prescribe Abx In Reflux”

- UTI in child <2-3mos of age
- VUR
- Instrumentation (urethral)
- Partial obstruction (eg UPJO, ureterocele)
- Prenatal hydronephrosis, awaiting investigations
- Awaiting radiologic tests after febrile UTI
- Immunosuppression
- Recurrent UTIs + normal GU tract

Indications for “early” GU imaging in kids

→ “UP UP Away”

- Unusual infecting organism
- Poor response to Abx treatment after 2-3 days
- Unknown source of infection
- Partial obstruction (known)
- Azotemia (newly Dx’d)

Syndromes associated with unilateral renal agenesis (URA)

→ “Frazer over Turned the Bus on DVP, Killed Many”

- Frazer’s syndrome
- Turner’s
- BOR syndrome
- DiGeorge syndrome
- VACTERL
- Poland’s syndrome
- Kallman’s
- Mayer-Rokitansky-Kuster-Hauser (MRKH)

Different forms of renal fusion anomalies

→ “I See Lumpy Logs Down South”

- Inferior (most common)
- S-shaped
- Lump or cake
- L-shaped
- Disc or donut
- Superior

Genetic syndromes associated with horseshoe kidney

→ “go TET the horsey”

- Turner’s
- Edward’s (trisomy 18)
- Townes-Brock

Complications of a horseshoe kidney

→ “SHUT the barn”

- Stones
- Hematuria
- UTIs
- Tumours } RCC, TCC, Wilm’s

Genetic and Non-heritable cystic diseases of the kidney

→ Genetic } “MC JAFA Man”

→ Non-heritable } “MB MASS-D”

- | | |
|---|--|
| - Multiple malformation syndromes (VHL, TS) | - MCDK |
| - Congenital nephrosis (AR) | - Benign multilocular cyst |
| - Juvenile nephronophthisis (AR) | - MSK |
| - AR PCKD | - Acquired renal cystic disease (ESRD) |
| - Familial glomerulocystic disease (AD) | - Simple cysts |
| - AD PCKD | - Sporadic glomerulocystic disease |
| - Medullary cystic disease (AD) | - Diverticulum of calyx |

Syndromes associated with MSK

→ “MSK is a BECH”

- BWS
- Ehler’s Danlos
- Caroli’s disease
- Hemi-hypertrophy

Diseases with renal cysts that have hyperplastic lining

→ “AVTA”

- AD PCKD
- VHL
- TS
- ARCD

GU anomalies associated with VUR

→ “Visa Has Reversed DUMMIED Charges”

- VACTERL
- Horseshoe kidney
- Renal agenesis (URA)
- Diverticulum (bladder)
- Ureterocele
- MCDK
- Megacystis-megaureter
- Imperforate anus
- Exstrophy
- Duplex system
- CHARGE

Indications to surgically correct VUR

→ “SHARP Blade Now”

- Scars (new)
- High grade VUR with scars
- Anomalies at UVJ (diverticulum, etc)
- Renal impairment } growth, function, etc
- Persisting into puberty or prior to pregnancy
- Breakthrough UTIs
- Non-compliance

Surgical options for VUR repair

→ “In pacific coast golf, Everyone Likes, Combined Play”

- Intravesical } Politano-Leadbetter
- } Cohen cross trigonal
- } Glenn-Anderson
- Extravesical } Lich-Gregoire
- Combined } Paquin

Syndromes associated with Prune Belly Syndrome

→ “Ed’s Belly Turned Prune”

- Edward’s syndrome (trisomy 18)
- BWS
- Turner’s
- Patau’s syndrome (trisomy 13)

DDx of dilated bladder on antenatal U/S

→ “PeePee Under Abdomen MAN”

- PBS
- PUVs
- Ureterocele (obstructing)
- Anterior obstruction (AUVs, syringocele)
- Megacystis-megaureter
- Atresia of urethra
- Neurogenic bladder

RFs for bladder exstrophy

→ “FAPPY”

- Family history
- ART used
- Parity (multip)
- Progesterone in T1
- Young mother

Conditions associated with PUVs

→ “P Vowels (AEIOU)”

- PBS
- Anemia
- Ejaculation abnormalities
- Infertility
- Osteodystrophy
- UDT

Contraindications to circumcision

→ “Hebrew’s Bris WISH ... Do Cx”

- Hypospadias
- Bleeding disorder
- Webbed or hidden penis
- Illness or jaundice
- Small penis
- Hydrocele or hernia (large)
- Dorsal hood deformity
- Chordee without hypospadias

RFs for UDTs

→ “Undescended Balls, Family Please ACCEPT Son”

- Underweight (low birth wt)
- Breech presentation
- Family Hx +ve
- Pre-term
- Asian descent
- Congenital anomalies
- C-section
- Estrogen exposure in utero
- Pre-eclampsia
- Twin
- Small for gestational age

Anomalies associated with UDT (incomplete list)

→ “Will U Prune Horse’s Hair Please?”

- Wilms’
- URA
- Prune Belly syndrome
- Horseshoe kidney
- Hypospadias
- PUVs

Intersex DSD classifications

→ Sex chromosomal DSD } “Killer XX Turned Pure but My Parts Vanished Too”

- Klinefelters (47,XXY)
- 46, XX
- Turner's (45,XO)
- Pure gonadal dysgenesis (XX or XY)
- MGD
- Partial gonadal dysgenesis
- Vanishing testis
- True hermaphrodite (Ovotestis DSD)

→ Masculinized female } “CAT”

- CAH
- Androgens (maternal)
- Tumours (ovarian or adrenal)

→ Undermasculinized male } “Let's Tell All 5 Men”

- Leydig cell agenesis
- Testosterone biosynthesis problem (StAR, 3 β HSD, 17 α -hydroxylase, 17,20 lyase, 17 β HSD)
- AIS (complete and partial)
- 5AR deficiency
- MIS problems (PMDS)

Features of Turner's syndrome

→ “BLLAC SiNNNS”

- | | |
|-------------------------|---|
| - Broad chest | - Short 4 th metacarpal bone |
| - Bicuspid aortic valve | - Nails (hypoplastic) |
| - Low-set ears | - Nipples are widespread |
| - Lymphedema at birth | - Nevi (pigmented) |
| - Aortic coarctation | - Neck (webbed) |
| - Cubitus valgus | - Short stature |

Investigations required in a child with ambiguous genitalia

→ “FUUKED Large, Then Gone After 17”

- FSH
- Urine for 17-ketosteroids
- Ultrasound
- Karyotype
- Electrolytes
- DHT
- LH
- Testosterone
- Genitography
- Anti-Mullerian hormone (MIS)
- serum 17-OH-progesterone & DOC

Main issues to discuss and consider when assigning gender to child with DSD

→ “Males And Females PMS”

- | | |
|-----------------------------|---------------------------------|
| - Malignancy risk of gonads | - Psychosocial outcomes |
| - Appearance overall | - Minimizing medical procedures |
| - Fertility potential | - Sexual function |

Chemotherapeutic regimes used for pediatric GU malignancies

→ Neuroblastoma } “PDEC”

- cisplatin
- doxorubicin
- etoposide
- cyclophosphamide

→ RMS } “VAC”

- vincristine
- actinomycin-D
- cyclophosphamide

→ Wilms' } “VADEC”

- vincristine
- actinomycin-D
- doxorubicin
- etoposide
- cyclophosphamide

→ RTK } “CEC”

- carboplatin
- etoposide
- cyclophosphamide

STONES

Urinary stone inhibitors

→ “GAG MI CUNT BRO”

- GAG
- Acid mucopolysaccharides
- Glucosamine
- Mg
- Inorganic pyrophosphates
- Citrate (most potent complexor of Ca)
- Urinary prothrombin fragment 1 (most potent inhibitor in normal urine)
- Nephrocalcin
- Tamm-Horsfall protein (most abundant protein in urine & most potent stone aggregation inhibitor)
- Bikunin
- RNA fragment
- Osteopontin

GU manifestations of sarcoidosis

→ “GU SARC Has Pulmonary Nodular Disease”

- Genital skin lesions
- Urolithiasis (Ca stones)
- Scrotal mass (epididymal or testicular)
- Azoospermia
- RPF
- CRF
- Hematuria
- Pseudotumour (renal)
- Nephrocalcinosis
- Detrusor areflexia, DSD, etc

*** extremely rare but can get bladder lesions that resemble malacoplakia } asteroid bodies, not Von Hanselmann or MG bodies ***

Indications for full metabolic stone work-up

→ “SICK SAP, U GO FOR URINE tests”

- Solitary kidney
- IBD
- Cystine stones
- Kids
- Struvite stones
- Anatomic abnormalities
- Pathologic skeletal fractures
- Uric acid stones
- Gout
- Osteoporosis
- Family history
- Occupation (eg pilots)
- Recurrent stone formers
- UTIs with stones
- Renal failure
- Infirm patients
- Nephrocalcinosis
- Ethnicity (eg Blacks)

Microscopic features of different stones

- | | | |
|---|----------------------------|---|
| - Ca phosphate-apatite | } amorphous | |
| - Ca PO ₄ dihydrate (brushite) | } needle-shaped | → “brushes have needle-shaped bristles” |
| - COM | } hourglass/dumbbells | → “you’d be a dumbell to SWL COM stones” |
| - COD | } tetrahedral, envelope | → “pay Cash-On-Delivery when your envelope arrives” |
| - struvite | } rectangular, coffin-lid | → “dead in a coffin if you get struvite stones” |
| - cystine | } hexagonal (benzene) | → “you are Hex’d since birth with cystine stones” |
| - uric acid | } amorphous shards, plates | → “shards of uric acid” |

Urine collection is tested as part of metabolic evaluation

→ “volume, creatinine to assess if adequate + COUCH + electrolytes”

- total volume
- creatinine
- Ca
- Oxalate
- Uric acid
- Citrate
- pH
- Na
- K
- Mg
- sulfate

Causes of hypocitraturia

→ “HARD TIP”

- HypoK
- Acidosis
- RTA (distal)
- Diarrheal states
- Thiazides
- Idiopathic
- Protein rich diet

Indications to investigate for RTA

→ “ACID Paint BRUSH”

- | | |
|----------------------------|---|
| - Azotemia | - Bilateral stones |
| - CaPO ₄ stones | - Recurrent stone formers (>2/yr) |
| - Infants with FTT | - Unexplained metabolic acidosis (NAG) |
| - Decreased K | - Sponge kidney (MSK, medullary nephrocalcinosis) |
| - Pyelo (chronic) | - Hypocitraturia |

Causes of acquired distal RTA

→ “POST CLAAASHH”

- | | |
|-------------------------|--|
| | - Cirrhosis |
| | - Lithium |
| - Pyelo (chronic) | - Analgesic abuse |
| - Obstruction (chronic) | - ATN |
| - Sick cell | - Autoimmune (thyroiditis, Sjogren's, SLE) |
| - Transplant (renal) | - Sarcoidosis |
| | - HyperPTH'ism |
| | - Hypercalciuria (familial) |

Ways that citrate reduces Ca stone formation

→ “Complex SNAG Protein”

- Complexes Ca
- Sedimentation inhibition
- Nucleation prevention
- Agglomeration inhibition
- Growth inhibition
- enhancement of Tamm-Horsfall Protein

RFs for uric acid stone formation

→ “They Make GOLDD’N PeePee”

- Thalessemia
- Myeloproliferative disorders
- Gout
- Obesity
- Lesch-Nyhan syndrome
- DM
- Dehydration
- Neoplastic disease
- Purine-rich diet
- Pregnancy

Disorders associated with cystinuria

→ “MR MD PHD”

- Mental retardation
- Retinitis Pigmentosa
- Muscular hypotonia
- Down syndrome (trisomy 21)
- Pancreatitis (hereditary form)
- Hemophilia
- DMD

RFs for struvite stones

→ “Urine Can OFFEND People”

- Urinary diversion
- Congenital GU tract malformation
- Obstructed GU tract
- Female
- FB (eg foley)
- Elderly
- Neurogenic bladder
- DM
- Premature infants

Bacteria that produce urease

→ “PACK PUSSY”

- | | |
|----------------------------|--------------------------|
| - Proteus | - Providencia |
| - Aeruginosa (Pseudomonas) | - Ureaplasma urealyticum |
| - Corynebacterium | - Staph. aureus |
| - Klebsiella | - Serratia |
| | - Yersinia |

Stones that are radiolucent on KUB

→ “U Don’t See The Xray IMAGE”

- Uric acid
- Dihydroxyadenine (DHA)
- Silicate
- Triamterene
- Xanthine
- Indinavir
- Matrix
- Ammonium acid urate
- Guafenasin
- Ephedrine

Medications that directly form stones

→ “Silicates GET u SIC”

- Silicate antacids
- Guafenasin
- Ephedrine
- Triamterene
- Sulfa
- Indinavir
- Cipro

Medications that promote stone formation

→ Can PLATE FAST

- Cytotoxic agents (tumour lysis → hyperuricemia)
- PO₄ binding antacids
- Laxatives
- Acetazolamide
- Thiazides
- Excess Vit D
- Furosemide
- Allopurinol
- Steroids
- Topiramate

Hereditary conditions associated with stones

→ “D = D, R = COAX Bart, X = X-Linked Hereditary Diseases

- AD } Distal RTA
- AR } Cystinuria
 - } Oxalosis (primary)
 - } Adenine (2,8-DHA)
 - } Xanthinuria
 - } Bartter’s
- X-linked } XR nephrolithiasis
 - } Lesch-Nyhan
 - } Hypophosphametic Rickets
 - } Dent’s disease

Causes of renal stones in neonates

→ “DUTTCH Stones in Really Little Suckers”

- | | |
|------------------------------|------------|
| - Dehydration | - Sepsis |
| - Underweight (low birth wt) | - RTA |
| - TPN | - Lasix |
| - Theophylline | - Steroids |
| - Cystinuria | |
| - HyperPTH’ism (familial) | |

Conservative recommendations to all first time stone formers

→ “Stone Formers Placed On Weight Control”

- Sodium in diet (restricted)
- Fluid intake (maintain ≥2L urine output daily)
- Protein in diet (moderated)
- Oxalate in diet (moderated)
- Weight loss
- Ca in diet (moderate)

Medications used for absorptive hypercalciuria

→ “Ty COB”

- Thiazides
- Cellulose PO₄
- Orthophosphates
- Bran

Medications used for primary hyperoxaluria

→ “Hong Kong? Don’t TEMPT”

- Hydration
- K citrate
- Dialysis
- Thiazides
- Elmiron
- Mg gluconate
- Pyridoxine (B6)
- Transplant (liver + kidney)

Medications used for enteric hyperoxaluria

→ “HONK My CIC”

- Hydration
- Oxalate restriction
- Na restriction
- K citrate
- Mg supplements
- Ca supplements
- Iron
- Cholestyramine

Mediations used for cystinuria

→ “PACK MAB”

- | | | |
|----------------------|---|-------------------|
| - Penicillamine D | \ | } chelators (S-S) |
| - Alpha-MPG (Thiola) | / | |
| - Captopril | / | } alkalinizers |
| - K citrate | \ | |
| - Mucomyst | / | } chelator |
| - Acetazolamide | / | |
| - Bucillamine | } | |

Theories behind mechanisms of stone fragmentation

→ “SSS CAD”

- Shear stress
- Spall fracture
- Superfocusing
- Compression
- Acoustic cavitation
- Dynamic fracture

Contraindications to SWL

→ “Habitual COUCH Potato”

- Habitus (obesity, orthopedic deformities)
- Coagulopathy
- Obstructed distally
- UTI
- Calcified renal artery aneurysm or AAA
- HTN uncontrolled
- Pregnancy

Indications to place stent prior to SWL

→ “SORRI, Stent Patient Before”

- | | |
|------------------------------|---------------------------|
| - Solitary kidney | - Size >1.5cm |
| - Obstruction prior to stone | - Poorly visualized stone |
| - Renal colic (refractory) | - Bilateral SWL |
| - Renal insufficiency | |
| - Infection + obstruction | |

RFs for acute renal injury after SWL

→ “TD COACH”

- Thrombocytopenia
- DM
- CAD
- Obesity
- Age (kids and elderly)
- Coagulopathy
- HTN

Indications to leave a stent after URS

→ “I Like Inserting Stents For Difficult Procedures”

- Infected + obstructed system
- Large stone burden with many fragments left to pass
- Impacted stone causing ureteral edema
- Solitary kidney
- Failure to advance due to narrow orifice or ureter
- Dilation of ureter performed
- Perforation

Indications to perform URS rather than SWL for a ureteric stone

→ “DR, SCOOP Fast Man”

- Dense stone (cystine or COM or brushite)
- Radiolucent stones
- Size >1cm
- Coagulopathy (uncorrected)
- Obese (morbid)
- Occupation → pilots must be stone-free
- Patient preference
- Failed SWL
- Multiple proximal ureteric stones

ADRENALS

Source of ectopic ACTH

→ “LP The BP”

- Lung Ca (most common)
- Pancreatic Ca
- Thymoma
- Benign bronchiolar adenoma
- Pheochromocytoma

Hereditary diseases associated with bilateral adrenal Ca

→ “CLiMB”

- Carney complex
- Li-Fraumeni
- Men 1
- BWS

Most common malignancies that metastasize to the adrenal glands

→ “MLB RCC ABC”

- Melanoma
- Lung Ca
- Breast Ca
- RCC
- contralateral adrenal
- Bladder
- Colon

Causes of adrenal insufficiency/Addison’s disease

→ “Adrenolytics MASH FAST”

- Adrenolytic meds
- Malignancy or mets
- Autoimmune (most common)
- Steroid withdrawal
- Hemorrhage from sepsis or HIT
- Fungal infections
- Atrophy
- Sarcoidosis
- TB

Genetic syndromes associated with pheochromocytoma

→ “2 Men Take Violent Anal from Weber’s Nasty Penis”

- MEN 2
- Tuberous Sclerosis
- VHL
- Ataxia-telangiectasia
- Sturge-WEBER
- Neurofibromatosis 1
- Paraganglioma

DDx for bilateral adrenal masses

→ “Mets PITCH Last”

- Metastases or malignancy
- Pheochromocytomas
- Infection
- TB
- CAH
- Hemorrhage
- Lymphoma

Features of MEN syndromes

→ “TP after PP”

MEN I }}} PTH + Pituitary + Pancreatic (islet cell)

MEN II }}} PTH + Thyroid + Pheo

MEN II }}} Thyroid + Pheo + ganglioneuromas + marfanoid

UPPER TRACT OBSTRUCTION

Causes of RPF

→ “RP TIMBIITS”

- RADs
- Periarthritis (eg AAA)
- Trauma
- Iatrogenic (surgery, etc)
- Meds
- Biliary disease
- Infectious (syphilis, TB, gonorrhea, etc)
- Inflammatory (eg IBD)
- Tumours (eg Lymphoma)
- Sarcoidosis

Medications that cause RPF

→ “PBL HHAMMER”

- Phenacetin
- β -blockers
- LSD
- Haldol
- Hydralazine
- Amphetamines
- Methylsergide
- Methyldopa
- Ergots
- Reserpine

Medications used for RPF

→ “STAMP C”

- Steroids
- Tamoxifen
- AZT
- MMF
- Penicillamine
- Cyclophosphamide

Diseases associated with RPF

→ “G JAWS”

- Glomerulonephritis (membranous)
- Juvenile RA
- Ankylosing spondylitis
- Wegener’s granulomatosis
- SLE (kids)

Causes of pear-shaped bladder

→ “U CAN Have Pelvic PEAR”

- Urinoma
- Cement extrusion from THR
- Aneurysm (common iliac)
- Neoplasm (liposarcoma, lymphoma)
- Hematoma
- Pelvic lipomatosis
- Psoas hypertrophy
- Edema
- Abscess
- Radiation fibrosis

Conditions associated with pelvic lipomatosis

→ “Weber’s Big Dick ROCS Vaginas”

- Weber-Christian disease
- Black
- Dercum’s disease (adiposis dolorosa)
- Retractable mesenteritis
- Obesity
- Cystitis glandularis
- Sclerosing lipogranulomatosis
- Venous obstruction (chronic)

Indications for surgical management of UPJO

→ “BRUSSHH”

- Bilateral
- Renal impairment
- UTIs
- Solitary kidney
- Stones
- Symptomatic (hematuria, pain, etc)
- Hydronephrosis worsening on serial imaging
- HTN (causal)

Drugs that inhibit ureteral peristalsis

→ “Not Action PACKed”

- NSAIDs
- α -blockers
- Progesterone
- ABx
- CCB
- K channel openers

Staging Systems – GU Malignancies & Trauma

ADULT MALIGNANCIES

Adrenal

Outline the staging of adrenal tumours.

T1	< 5 cm, localized to adrenal
T2	≥ 5 cm, localized to adrenal
T3	Local invasion, no adjacent organ
T4	Adjacent organ invasion
N1	Regional nodes
M1	Distant mets
Stage I	T1NoMo
Stage II	T2NoMo
Stage III	T3 or N1
Stage IV	T4, T3N1Mx, or M1

Renal

What is the TNM staging system of RCC (2002)?

1) T → TX – can't assess primary

To – no primary

T1a – tumour <4cm and confined to kidney

T1b – tumour 4-7cm and confined to kidney

T2 – tumour >7cm and confined to kidney

T3a – tumour invades adrenal or perinephric fat but NOT outside Gerota's

T3b – tumour extends into segmental veins, renal vein, or IVC below diaphragm

T3c – tumour extends into IVC above diaphragm or invades wall of IVC

T4 – tumour invades beyond Gerota's

2) N → NX – can't assess LNs

No – no regional LNs

N1 – mets to single regional LN

N2 – mets to >1 regional LN

3) M → MX – can't assess

Mo – no mets

M1 – mets

4) Stage grouping

→ stage I	T1	No	Mo
stage II	T2	No	Mo
stage III	T1 or T2	N1	Mo
	T3	No or N1	Mo
Stage IV	T4 or N2 or M1		

→ RCC <4cm do significantly better (Frank et al. J Urol '04 p1652)

→ 7cm was mean tumour size in SEER database

→ invasion of renal sinus fat (T3a) may in fact be worse than venous thrombus (T3b/c)

→ adrenal extension (T3a) should likely be classified as T4

→ indirect adrenal involvement (T3a) might be better classified as M1

Upper tract TCC

What is the TNM staging system for upper tract TCC?

- T Stage
 - Ta – papillary noninvasive
 - Tis – CIS
 - T1 – invades subepithelial connective tissue (lamina propria)
 - T2 – invades into muscularis propria
 - T3 – invades into periureteral fat, perinephric fat, or into renal parenchyma
 - T4 – invades adjacent organ or through kidney into perinephric fat
- N Stage
 - N1 – mets to single LN (≤ 2 cm)
 - N2 – mets to single LN (2-5cm) or multiple LNs (all < 5 cm)
 - N3 – mets to LN > 5 cm
- M Stage
 - M1 – distant mets

What is the AJCC staging system of upper tract TCC?

- stage 1 } anything $< T2$ and No, Mo
- stage 2 } $T2$ and No, Mo
- stage 3 } $T3$ and No, Mo
- stage 4 } $T4$ or any T and N+, M+

***** UPPER TRACT TCC TENDS TO BE UNDERSTAGED *****

Bladder

What is the 1997 AJCC TNM staging of bladder cancer?

- T }
 - Ta – papillary
 - Tis – flat CIS
 - T1 – lamina propria invasion
 - T2a – superficial muscularis propria invasion
 - T2b – deep muscularis propria invasion
 - T3a – microscopic extension into perivesical fat
 - T3b – macroscopic extension into perivesical fat
 - T4a – invading pelvic viscera (eg prostatic stroma, vaginal wall, rectum, uterus)
 - not fixed
 - T4b – invading pelvic side wall, abdo wall, bony pelvis
 - fixed
- N }
 - No – no pelvic node mets
 - N1 – single node ≤ 2 cm below common iliacs
 - N2 – single node 2-5cm or multiple small nodes (< 5 cm)
 - N3 – node > 5 cm
- M }
 - Mo – no distant mets
 - M1 – distant mets

Prostate

What is the TNM staging of PCa (2002 AJCC)?

→ T stage

- T1a } PCa found after TURP with <5% involved or <Gleason 7
- T1b } PCa found after TURP with >5% involved or ≥Gleason 7
- T1c } PCa found on TRUS Bx
- T2a } palpable PCa involving ≤50% of one lobe
- T2b } palpable PCa involving >50% of one lobe
- T2c } palpable PCa involving both lobes
- T3a } ECE
- T3b } SV invasion
- T4 } invasion of BN, external sphincter, rectum, levators, and/or pelvic wall

→ N stage

- N1 } mets in regional LNs *** old system had N1, N2, N3 based on # and size of nodes***

→ M stage

- M1a } involvement of non-regional LNs
- M1b } involvement of bones
- M1c } involvement of other distant sites

What is the T stage classification for TCC of the prostate?

- Tis-pu } CIS involving prostatic urethra
- Tis-pd } CIS involving prostatic ducts
- T1 } invades subepithelial connective tissue
- T2 } invades prostatic stroma, corpus spongiosum, or periurethral muscle
- T3 } invades corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
- T4 } invades adjacent organs (invasion of bladder)

Testicular

What is the 2008 AJCC TNMS Staging system for testicular cancers?

- see chart below } **updated from 1997 AJCC TNM**
- **60% of all men with testicular GCTs present with stage 1 disease**
→ stage 1 more common with seminoma (~70%) than NSGCTs (30%)

PRIMARY TUMOUR (pT)

pTo	no evidence of primary tumour
pTis	ITGCN (CIS)
pT1	limited to testis & epididymis without LVI → can invade tunica albuginea, but not tunica vaginalis
pT2	limited to testis & epididymis + LVI or extending into tunica vaginalis
pT3	invades spermatic cord +/- LVI
pT4	invades scrotum +/- LVI

CLINICAL REGIONAL LNs (cN)

No	no regional LN mets
N1	LN ≤2cm or multiple LNs all <2cm
N2	LN 2-5cm or multiple LNs all 2-5cm
N3	LN >5cm

PATHOLOGIC REGIONAL LNs (pN)

pNo	no regional LN mets
pN1	LN ≤2cm or ≤5 LNs all <2cm
pN2	LN 2-5cm or >5 LNs all <5cm or evidence of extranodal extension
pN3	LN >5cm

DISTANT METS (M)

Mo	no distant mets
M1a	non-regional nodal or lung mets
M1b	distant mets

SERUM TUMOUR MARKERS (S)

So	all markers normal
S1	LDH <1.5x N + AFP <1000 + βhCG <5000
S2	LDH 1.5-10x N + AFP 1000-10,000 + βhCG 5000-50,000
S3	LDH >10x N + AFP >10,000 + βhCG >50,000

What is the AJCC Stage Grouping system for testicular cancer?

Stage Grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	T1–T4	N0	M0	SX
Ia	T1	N0	M0	S0
Ib	T2	N0	M0	S0
	T3	N0	M0	S0
	T4	N0	M0	S0
Is	Any T	N0	M0	S1–S3
Stage II	Any T	Any N	M0	SX
IIa	Any T	N1	M0	S0
	Any T	N1	M0	S1
IIb	Any T	N2	M0	S0
	Any T	N2	M0	S1
IIc	Any T	N3	M0	S0
	Any T	N3	M0	S1
Stage III	Any T	Any N	M1	SX
IIIa	Any T	Any N	M1	S0
	Any T	Any N	M1	S1
IIIb	Any T	Any N	M0	S2
	Any T	Any N	M1	S2
IIIc	Any T	Any N	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S

Penile

What is the TNM staging system for penile cancer?

- no universally excepted staging system
- TNM still best (AJCC 1997)
- Primary Tumour (T)
 - TX → not assessed
 - To → no evidence of tumour
 - Tis → CIS
 - Ta → noninvasive verrucous carcinoma
 - T1 → into subepithelial connective tissue
 - T2 → into corpus cavernosum or spongiosum
 - T3 → into urethra or prostate
 - T4 → into adjacent structures
- Lymph nodes (N)
 - NX → not assessed
 - No → no evidence of tumour
 - N1 → mets to single superficial regional LN
 - N2 → mets in multiple or B/L superficial LNs,
 - N3 → mets to deep inguinal or pelvic LNs
- Distant Mets (M)
 - MX → not assessed
 - Mo → no evidence of tumour
 - M1 → distant mets

*** **EXTENT OF LN METS IS MOST IMPORTANT PROGNOSTIC FACTOR** ***

Describe the stage groupings for penile cancer

- Stage I → **T1** NoMo
- Stage II → **T2** No-1Mo or **T1N1** Mo
- Stage III → **T3** No-2 Mo or **T1-2N2** Mo
- Stage IV → **T4**No-3 Mo or **T1-4N3** Mo or **T1-4No-3M1**

Urethra

What is the TNM staging system for urethral cancer?

- T stage
 - Ta } papillary, polypoid, or verrucous carcinoma
 - Tis } CIS
 - T1 } invades subepithelial connective tissue
 - T2 } invades corpus spongiosum, prostate, or periurethral muscle
 - T3 } invades corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
 - T4 } invades adjacent organs
- N stage
 - N1 } mets to single LN ≤2cm
 - N2 } mets to single LN 2-5cm or multiple LNs all <5cm
 - N3 } mets to LN >5cm
- M stage
 - M1 } distant mets

PEDIATRIC MALIGNANCIES

Neuroblastoma

What is the staging system used for neuroblastoma?

- **International Neuroblastoma Staging System (INSS)**
- **based on clinical, radiographic, & surgical evaluation**
- determines intensity of CHEMO and RADs } especially for intermediate risk group
- Stage 1 } localized tumour + **complete excision** + ipsilateral LNs -ve
 - LNs attached to & removed with primary can be positive
- Stage 2A } localized tumour + **incomplete excision** + ipsilateral LNs -ve
- Stage 2B } localized tumour +/- complete excision + **ipsilateral LNs +ve**
- Stage 3 } **unresectable tumour crossing midline** +/- regional LN involvement
 - OR localized unilateral tumour + contralateral regional LNs +ve
 - OR midline tumour + bilateral extension
- Stage 4 } any tumour + **distant mets** (LNs, bone, BM, liver, skin, etc)
- Stage 4S } localized primary + **distant mets only in skin, liver, and/or BM (<10%)**
in infants <1yr of age (NO BONE METS)
 - many of these tumours undergo spontaneous regression

Wilms'

What is the COG Staging system used for Wilms' tumour?

- **Children's Oncology Group (N. American approach to Wilms' tumours)**
- **based on surgical & histopathologic findings**
- presence of nephrogenic rests no included in staging
- Stage 1 } limited to kidney + completely excised + intact renal capsule + no rupture
- Stage 2 } tumour beyond kidney + completely excised +/- extrarenal vessel thrombus
- Stage 3 } residual tumour confined to abdomen
 - incomplete excision OR +ve LNs OR tumour spillage OR peritoneal implants OR tumour rupture
 - Biopsy makes automatically stage 3
- Stage 4 } hematogenous mets to lung, liver, bone, brain, etc
- Stage 5 } bilateral renal involvement

RMS

What is the IRSG TGNM staging system used for RMS?

- based on clinical, radiographic, laboratory & histologic evaluation
- old system included surgical resection details (like neuroblastoma)
- Stage 1 } **favorable site** (paratesticular, vagina) + no mets
- Stage 2 } **unfavorable site** (prostate, bladder) + small (<5cm) + -ve LNs + no mets
- Stage 3 } **unfavorable site** (prostate, bladder) + **big (>5cm) OR +ve LNs** + no mets
- Stage 4 } any site + **evidence of mets**
- T stage
 - T1 } confined to site of origin
 - T2 } fixation to surrounding tissues
 - <5cm
 - >5cm
- G stage
 - G1 } favorable histology (embryonal, botryoid variant, spindle cell variant)
 - G2 } unfavorable histology (alveolar, undifferentiated, pleiomorphic)
- N stage
 - No } no regional LN disease
 - N1 } regional LNs +ve clinically
- M stage
 - Mo } no distant mets
 - M1 } +ve mets

TRAUMA

Renal

What is the AAST classification of renal injuries?

- grade 1 } renal contusion (hematuria + N imaging)
 OR subcapsular hematoma (nonexpanding)
 - grade 2 } nonexpanding perirenal hematoma (confined to retroperitoneum)
 OR laceration (<1cm)
 - grade 3 } laceration >1cm WITHOUT violation of collecting system or urinary extravasation
 - grade 4 } laceration into collecting system
 OR main renal artery or vein injury w/ contained hemorrhage (including segmentals)
 - grade 5 } shattered kidney
 OR avulsion of renal hilum (devascularized kidney)
- *** advance one grade for bilateral injuries, up to grade 3 ***

Ureter

What is the classification of ureteral trauma (NEW)?

- AAST
- grade 1 } contusion or hematoma without devascularization
 - grade 2 } <50% transection
 - grade 3 } ≥50% transection
 - grade 4 } complete transection with <2cm devascularization
 - grade 5 } avulsion with >2cm devascularization
- *** if bilateral, advance one grade up to grade 3 ***

Bladder

How do you classify bladder injuries?

- 1) contusions
- 2) extraperitoneal (65%)
- 3) intraperitoneal (25%)
- 4) combined extraperitoneal & intraperitoneal (10%)

AAST bladder

Grade		Description
I	Hematoma	Contusion, intramural hematoma
I	Laceration	Partial thickness
II	Laceration	Extraperitoneal bladder wall laceration < 2 cm
III	Laceration	Extraperitoneal (>2 cm) or intraperitoneal (<2 cm) bladder wall laceration
IV	Laceration	Intraperitoneal bladder wall laceration >2 cm
V	Laceration	Intraperitoneal or extraperitoneal bladder wall laceration extending into the bladder neck or ureteral orifice (trigone)

Urethral

What is the OLD Colapinto classification of urethral injuries?

- J Urol 1977
- type I } urethral **stretch** injuries
- type II } membranous urethral **disruption proximal to GU diaphragm**
- type III } membranous urethral **disruption both proximal and distal to GU diaphragm**

What is the AAST classification of posterior urethral injuries?

- class 1 } blood at meatus, but normal imaging
- class 2 } stretch injury without extravasation
- class 3 } partial disruption (contrast goes into bladder)
- class 4 } complete disruption w/ separation <2cm
- class 5 } complete disruption w/ separation ≥ 2 cm or if concomitant vaginal, rectal, prostatic injury

What is the Goldman classification of urethral injuries?

- class 1 } stretch injury
- class 2 } distraction injury above GU diaphragm
- class 3 } distraction across GU diaphragm into bulbar urethra
- class 4a } distraction of BN into proximal urethra
- class 4b } distraction of bladder base
- class 5 } isolated anterior urethral injury